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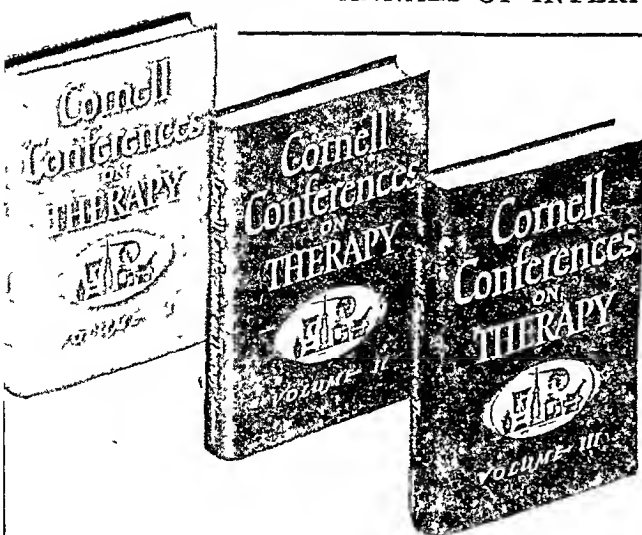
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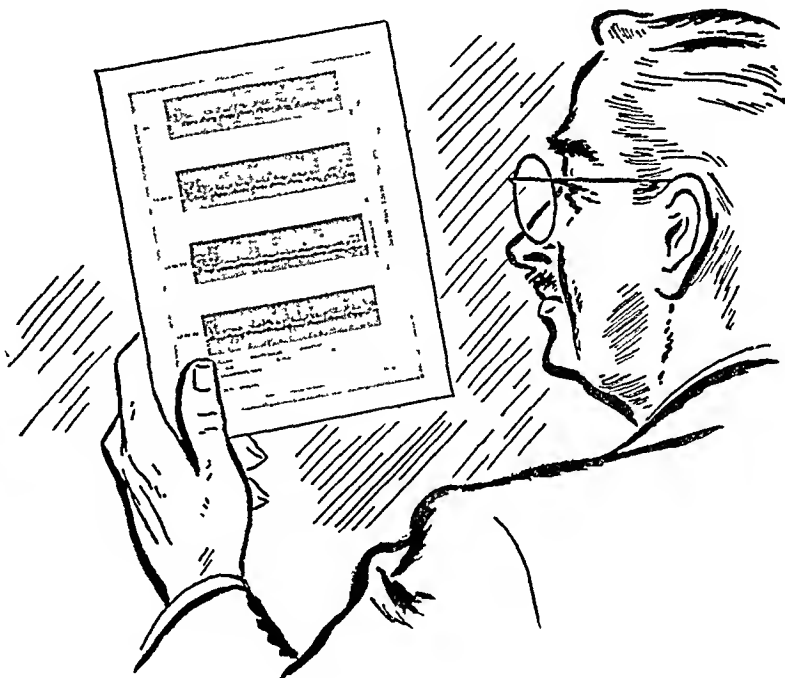
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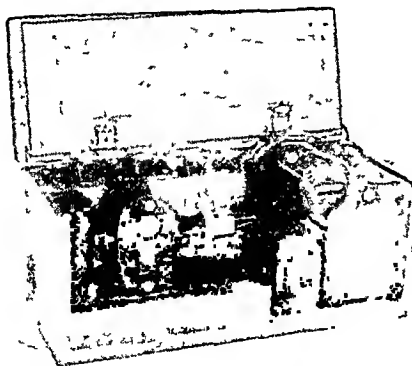
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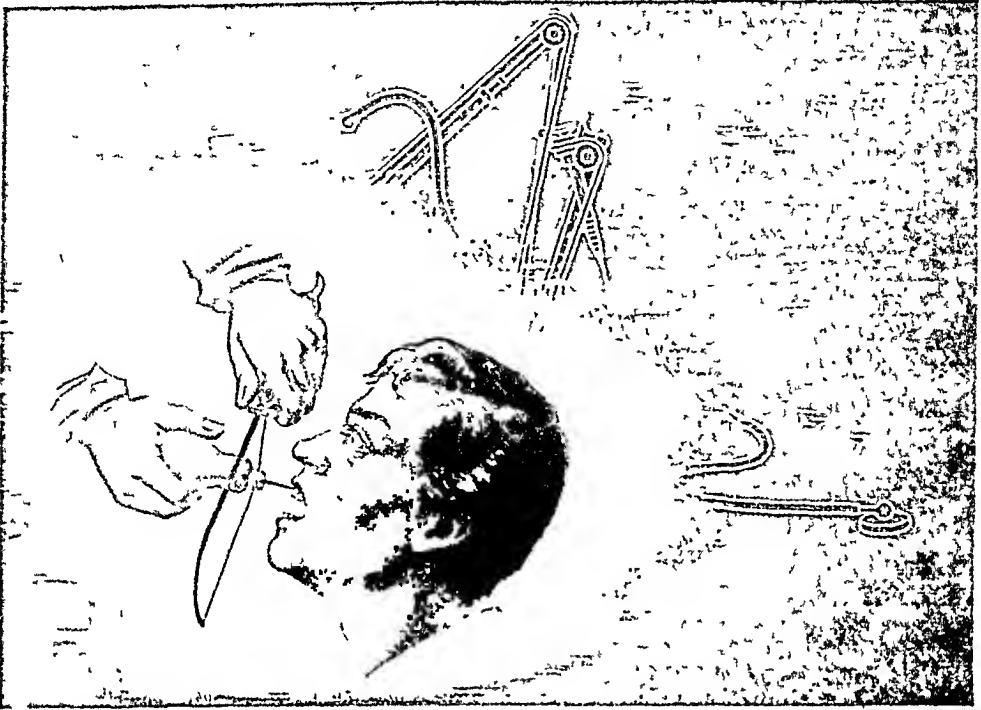
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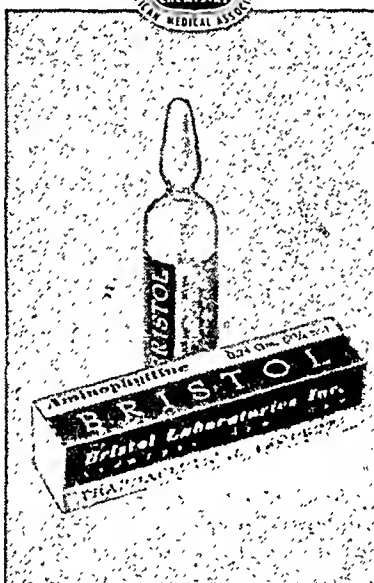
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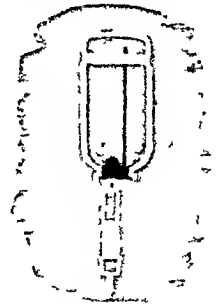
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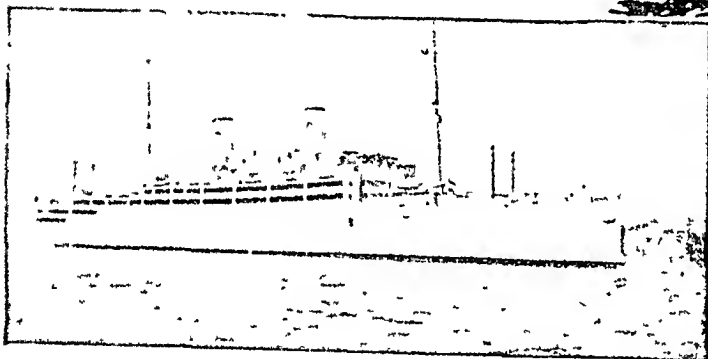
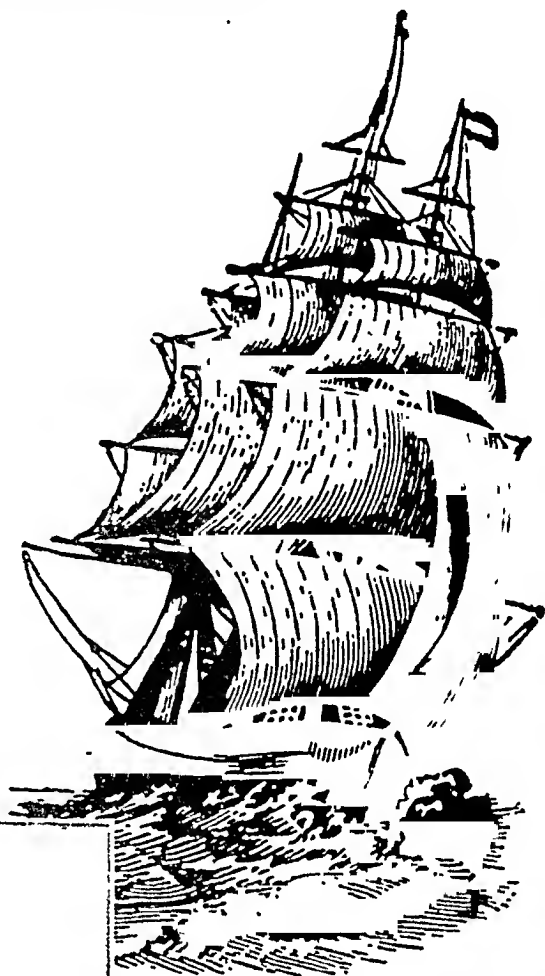
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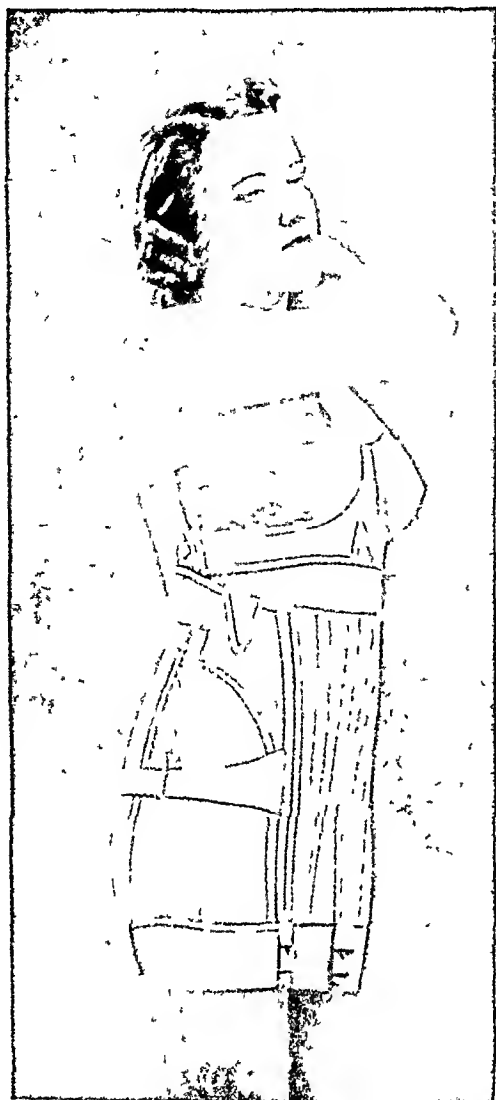
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Rakoff, A. E., Paschke, K. E. and Cantarow, A.: A Clinical Evaluation of Dienestrol, A Synthetic Estrogen, J. Clin. Endocrinol., 7:688 (Oct.) 1947.

### *Low toxicity*

"This low incidence of nausea [1.3 per cent] is . . . in contrast with that encountered during treatment with other synthetic estrogens."

Finkler, R. S. and Becker, S.: "A Preliminary Evaluation of Dienestrol in the Menopause, Am. J. Obst. & Gynec., 53:513 (Mar.) 1947.

### *Low recommended dosage*

"Clinical trials . . . indicate that doses of 0.2 to 0.5 mg. daily are adequate, dependable and tolerated . . ."

Sikkema, S. H. and Sevringhaus, E. L.: Dienestrol: Another Synthetic Estrogen of Clinical Value, Am. J. Med., 2:251 (Mar.) 1947.



*White's*

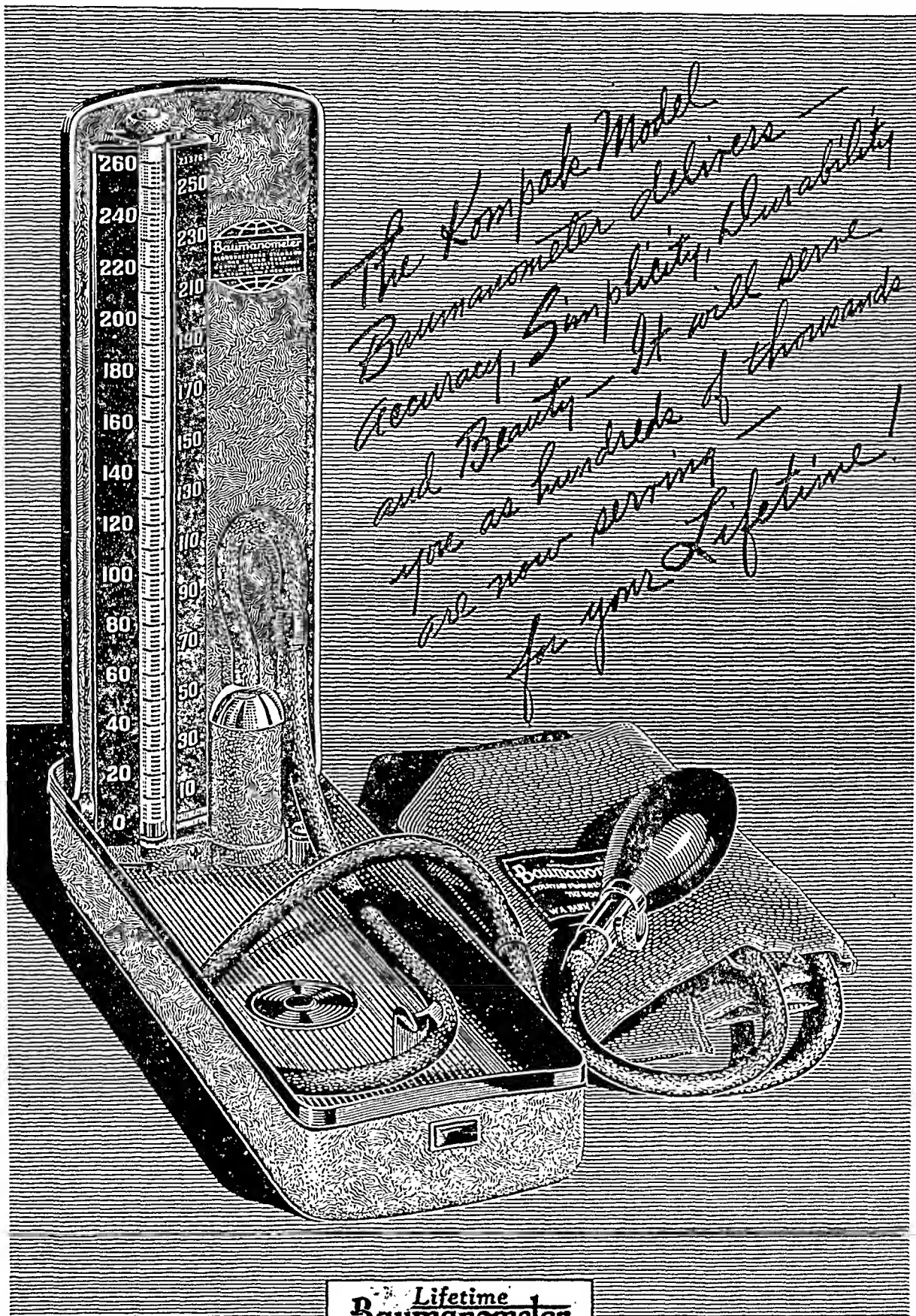
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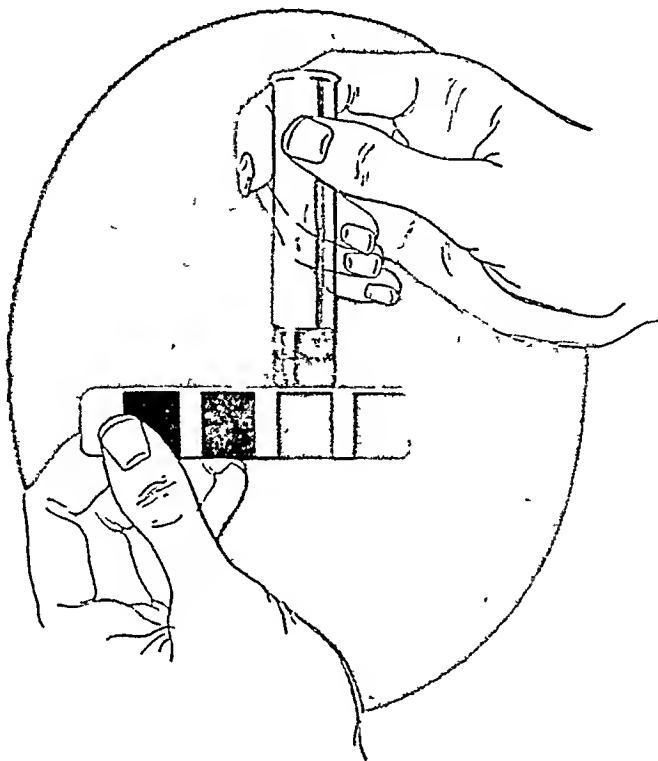
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Accuracy, Simplicity, Durability  
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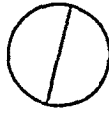
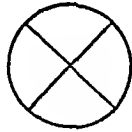
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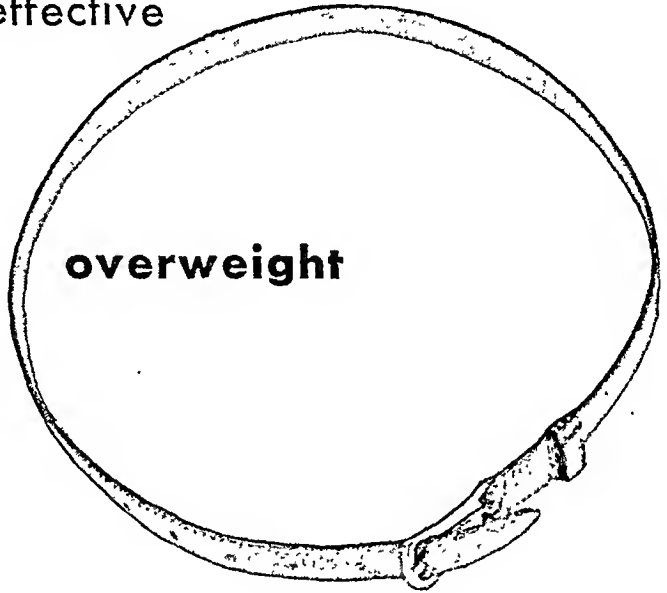
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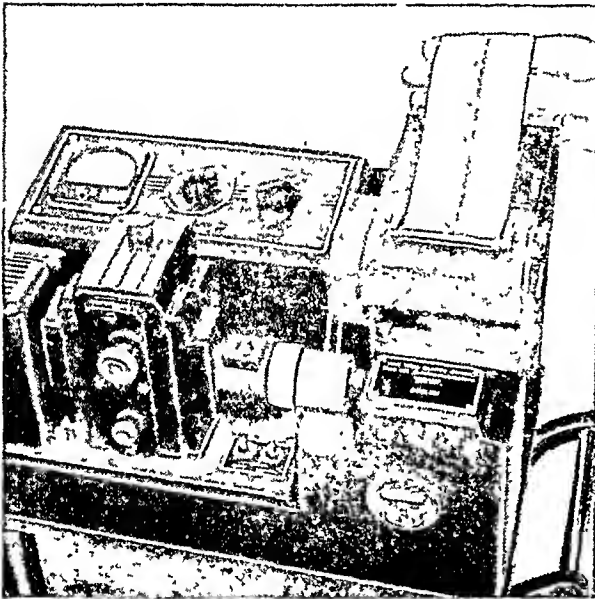
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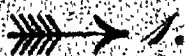
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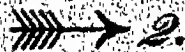
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possessing all the therapeutic virtues  
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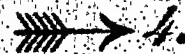
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Improved tolerance because its freedom  
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3.

Slow or rapid digitalization: the drug is  
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Greater safety, because rapid excretion  
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5.

Greater flexibility in maintenance: con-  
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until the desired effect is obtained.

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**Oral Preparations:** Tablets brand  
Digoxin, 0.25 mgm. (gr. 1/240)  
approx. 1 Bottle of 25, 100 and 500

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Digoxin Injection,  
0.5 mgm. (gr. 1/120 approx.) in 1 cc.  
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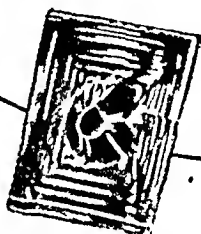
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**CRYSTALLINE PENICILLIN G POTASSIUM**



Each foil wrapped tablet contains 50,000 units, the usual single dose.



The tablet is simply dropped into the nebulizer,



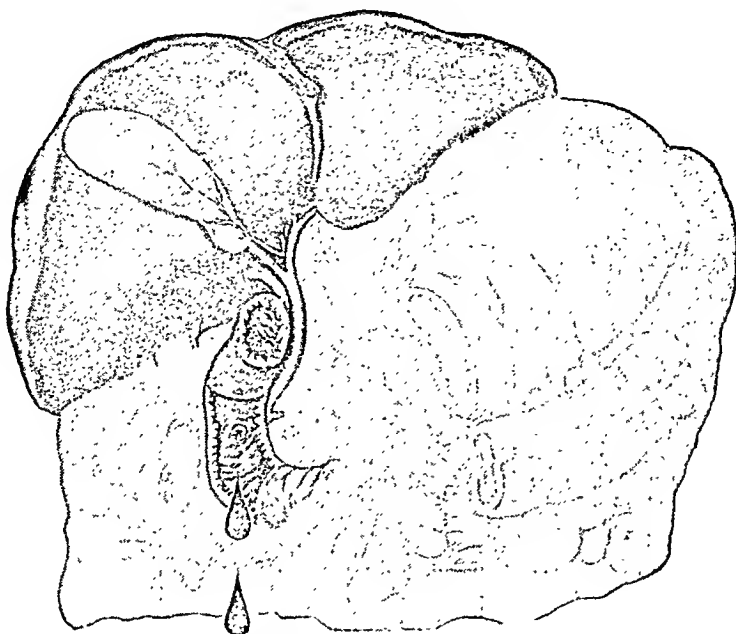
10 to 15 minims of water or saline solution are added with a dropper,



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Decholin in  $3\frac{3}{4}$  gr. tablets. Boxes of 25, 100, 500 and 1000.

\*Albrecht, F. K.: *Modern Management in Clinical Medicine*, Baltimore, The Williams and Wilkins Co., 1946, p. 170.

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new and ONLY sodium-free  
salt substitute that tastes  
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that makes food taste exactly like  
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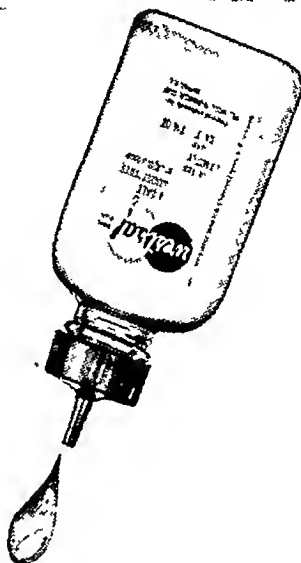
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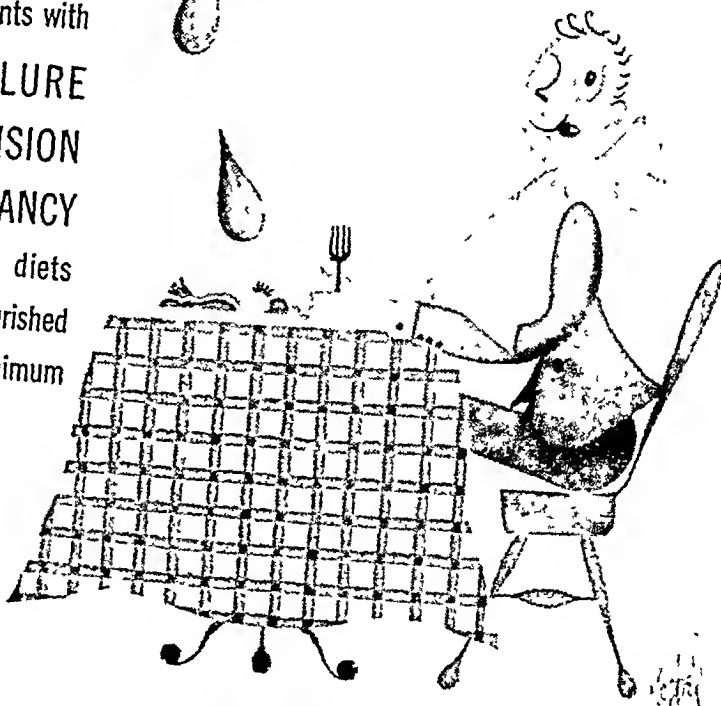
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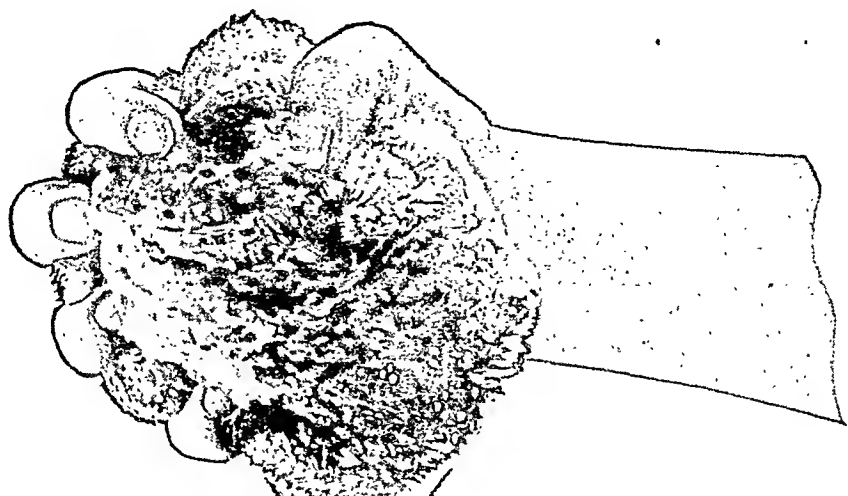
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Enteric coated tablets for oral use.

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\*Based on average reported values for milk.



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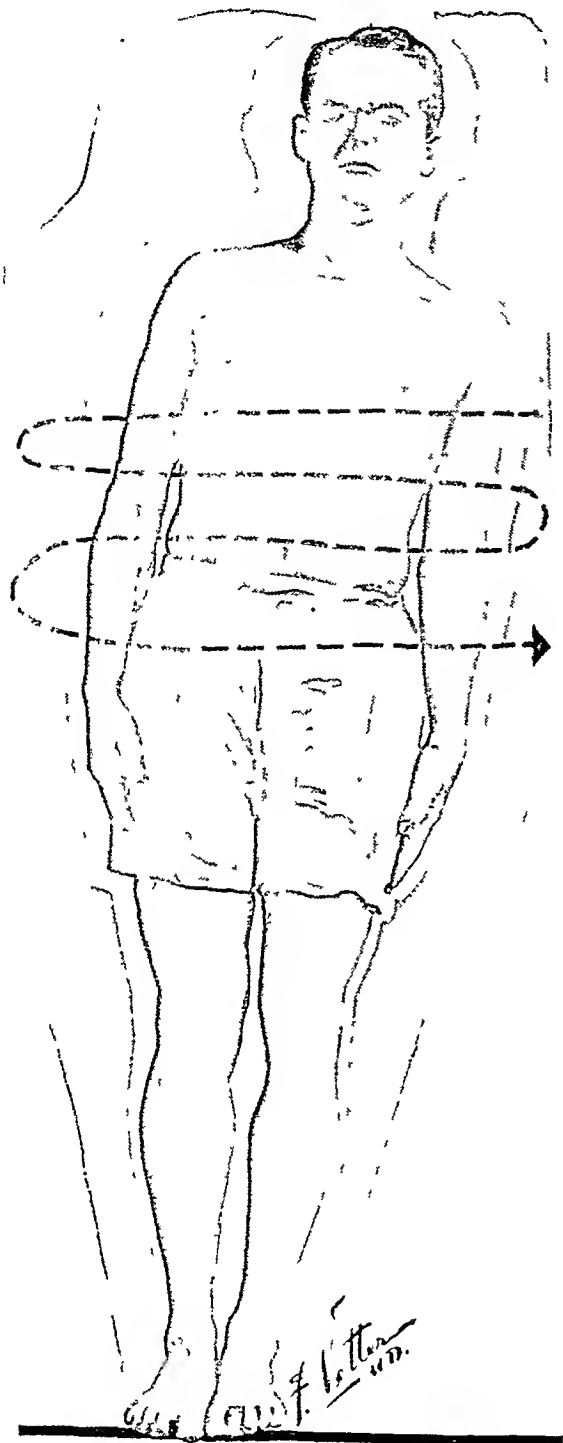
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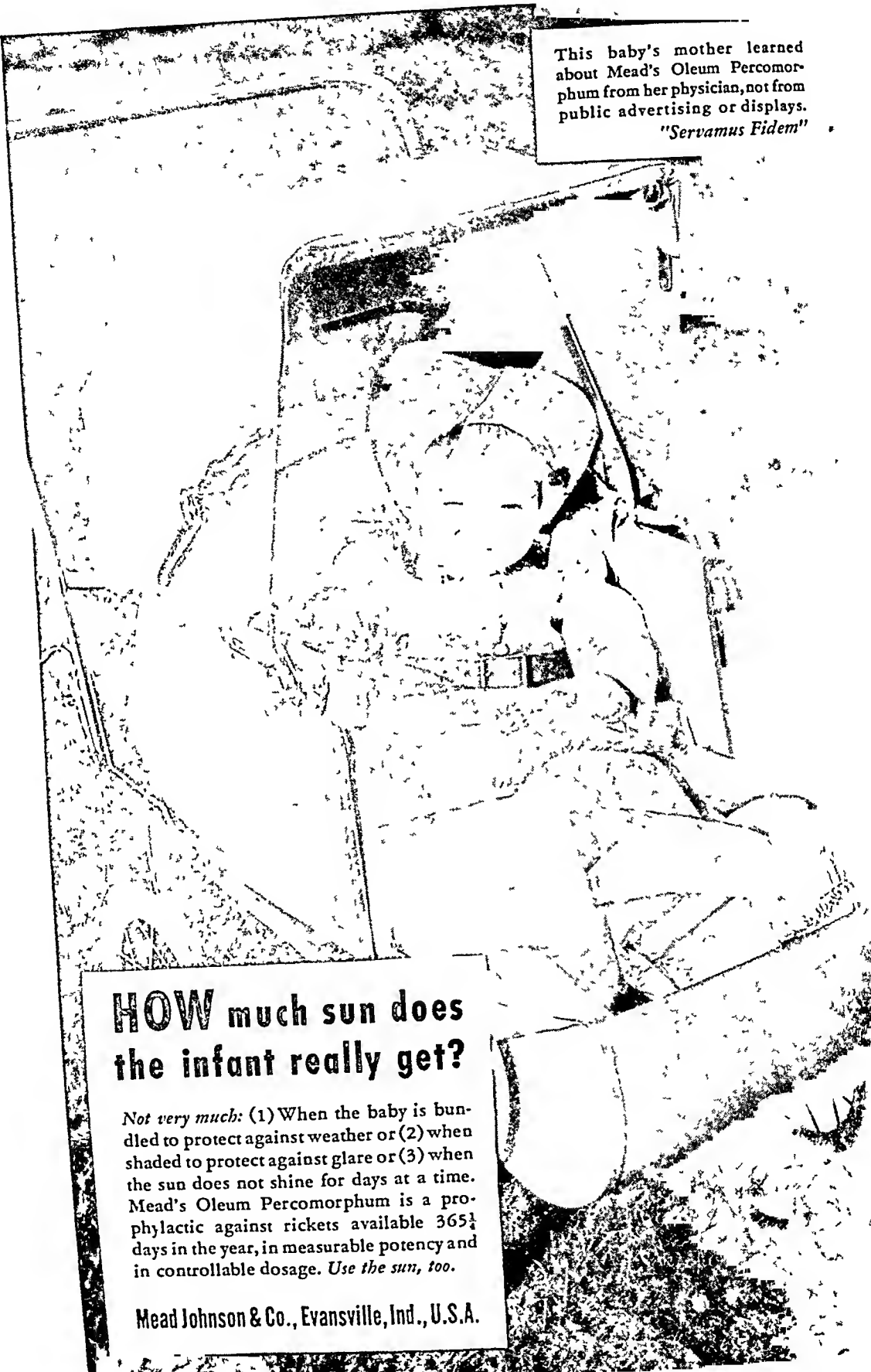
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1. J.A.M.A., 131:826, 1946

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Mead Johnson & Co., Evansville, Ind., U.S.A.

# ANNALS OF INTERNAL MEDICINE

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VOLUME 29

OCTOBER, 1948

NUMBER 4

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## PATHOGENESIS OF RHEUMATIC FEVER \*

By WM. J. KERR, M.D., F.A.C.P., *San Francisco, California*

RHEUMATIC fever is one of our most serious diseases. It attacks children primarily but under conditions of crowding, exposure, and fatigue, may affect older age groups in certain localities as was demonstrated in the recent war. The late manifestations of the disease are so disabling that they produce our most serious medical economic and social problems in the prime of life for those so afflicted.

There is abundant evidence that microorganisms of the *streptococcus* group are the etiological agents which initiate a train of reactions in the host resulting in the lesions characteristic of the disease. It is not proved that a single strain of streptococci is the specific agent, although beta-hemolytic streptococci of one or more specific types are generally isolated from the throat of patients early in the course of the disease in different outbreaks. The many points of similarity to the pathogenesis of scarlet fever, where certain strains of beta-hemolytic streptococcus are almost undeniably the etiological agents, support the view that types of streptococci initiate the immunological mechanisms in rheumatic fever. The appearance and fluctuations in specific streptolysin titers in patients appears also to be of significance, although this and other immunity reactions may appear in persons who show no clinical evidence of the localizations of rheumatic fever in the tissues. A significant difference between rheumatic fever and scarlet fever lies in the frequency with which pyogenic lesions appear in the latter in the lymphatic tissues and throughout the body. The streptococci in scarlet fever appear to provoke not only a more violent general reaction with outward manifestations in the skin and lymph nodes, but also more evidence of invasion by the organisms than is generally observed in rheumatic fever.

The seasonal occurrence of outbreaks of rheumatic fever at the time of year when streptococcal infections are prevalent lends further support to the

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\* Presented before the 29th Annual Session of the American College of Physicians, April 22, 1948, San Francisco, California.

From the Division of Medicine, University of California Medical School, San Francisco, California.

view that these organisms are etiological factors. It is apparent from observations made in military installations during the recent war that certain localities show a higher attack rate for rheumatic fever than others under conditions of congregation, housing, clothing, physical activity and dietary habits, which are common to all similar installations. While inclement weather (more often experienced in temperate climates) may be an important factor, it would appear that the conditions favorable for the beta-hemolyticus streptococcus are of determining significance.

The *rôle of under nutrition* in general, and of the accessory dietary factors in particular, is difficult to evaluate. In civil life the high prevalence of rheumatic fever among those in the lower economic brackets may indicate only generally lowered resistance to infection. There is evidence that a deficiency of accessory dietary factors is widespread in this economic group. The tendency to purpuric manifestations appears to be high at the season when rheumatic fever is prevalent, and vitamin C content of the blood at such times is generally low. The hemorrhagic tendency is a feature of the symptom complex of rheumatic fever and may be readily controlled by supplemental intake of this vitamin. Although it must be assumed that general nutrition is inadequate, and that other factors than vitamin C may be of importance, it is possible that the vascular integrity of those attacked is faulty, thus rendering tissues vulnerable to injury.

The *portal of entry* is generally assumed to be the upper respiratory tract, although if the streptococcus is the etiological agent, we must assume that any site where the organisms gain a foothold may serve as a portal. There is scant evidence that the streptococcus actually spreads beyond the pharyngeal wall, the tonsils, and other local lymphatic structures, or at times, the peritonsillar tissues. The occasional demonstration of streptococci in synovial fluids and elsewhere in body fluids, and tissues in patients with rheumatic fever and many other diseases, is not surprising in view of the ubiquitous nature and varying pathogenicity of these organisms. The almost constant failure to find the same type specific streptococci in the throat and in the tissues generally involved suggests that the reactions throughout the body are in response to substances produced locally in the pharynx, and acting through humoral mechanisms on distant tissues. If the substance produced locally is cytotoxic, it is obvious that it differs somewhat from the toxic material responsible for the more violent systemic reactions and the dermatological responses in scarlet fever.

The *silent period* of some days to two or three weeks following the pharyngeal symptoms is one of the striking and characteristic features of rheumatic fever. A similar pause is observed in scarlet fever before the renal, articular and cardiac manifestations appear. It is during this period that immune mechanisms are set in motion. An increased antistreptolysin titer is almost constantly observed.

The *clinical manifestations* of varying severity then make their appearance in the synovial membranes and other connective tissues, in the cardiac

valves, myocardium and pericardium, in the skin, brain, lungs, and kidneys, with symptoms and signs peculiar to the organs and structures concerned. Other involvements are more subtle, seldom causing revealing symptoms and signs, but it is apparent from cytological studies that lesions are widespread and bear an intimate relationship to the vascular and perivascular structures. The systemic symptoms including fever, leukocytosis and rapid sedimentation of red blood cells are not peculiar to rheumatic fever but common to many infectious diseases.

The *course* of rheumatic fever is variable. There is a tendency to chronicity and seasonal recurrence and during recurrent attacks the pattern of symptoms and signs in a given patient is not always repeated. In fact, over a period of years, episodes of reactivity in the cardiac structures particularly may appear without systemic symptoms of an infection, or other symptoms in the joints, or elsewhere. A small percentage of persons with advanced valvular disease of rheumatic origin may have had no history of preceding illness resembling rheumatic fever. Many patients with rheumatic cardiac disease of long standing, who present themselves with myocardial failure and abnormal mechanisms, will show at necropsy histological evidence of rheumatic activity.

The *lesions* of rheumatic fever are of microscopic size and diffusely located in relation to smaller blood vessels. It is held by many that the lesions are as specific for rheumatic fever as the tubercle is specific for tuberculosis. It is obvious that neither assumption is correct. However, the Aschoff body when found in the tissues of a patient with other evidence of rheumatic disease supports the diagnosis, but we must consider other types of vascular disease which clinically differ from rheumatic fever, e.g., lupus erythematosus disseminata, and periarteritis nodosa particularly. The reactions in the synovial membranes, subcutaneous tissues, cardiac valves, cardiac muscle, pericardium, lungs and brain, differ in the degree of exudation so markedly that in some tissues the cellular components are not arranged in the compact masses which are seen so characteristically in the myocardium. The tissue reaction occurs as a small necrotic area around the small blood vessels and is made up of polymorphonuclear leukocytes and cells with a large basophilic cytoplasm. The latter cells are often multinuclear. There is a localized increase in vascularity. As the lesion progresses plasma cells and fibroblasts appear, gradually replacing the basophilic cells. The end-result is a small area of fibrosis. The only tissues where lesions cause damage of a permanent, progressive and crippling nature are in the heart. Why the proliferative features of the process assume such significance in the heart is unknown. The organization of the lesions in the valves and pericardium leads to mechanical disturbances which affect hemodynamics and lead to myocardial failure. The joints are seldom affected permanently. The kidneys may suffer chronic and progressive injury.

The *treatment* of rheumatic fever is generally unsatisfactory. The studies of Chandler and Taussig suggests that continuous or seasonal use

of small daily oral doses of the sulfonamide drugs may prevent recurrences or first attacks by reducing the attack rate of hemolytic streptococcus infection. Removal of the tonsils may prevent initial attacks of rheumatic fever but this procedure apparently has no effect in preventing recurrences. Removal to a warmer and more equable climate may be beneficial in preventing recurrences, chiefly, it would appear, from the chance it offers of escape from streptococcal exposure. The salicylate drugs are useful in controlling the systemic reactions and in reducing the symptoms and signs related to the exudative process, but there is little evidence that the over-all course of the disease or the end-results are altered by this or any other drug now available. The heroic use of antibiotics and salicylates during the recent war did not result in a cure of the process in the tissues. Other methods of active treatment have also been found wanting. It is probable that once the "trap is set" by the streptococcus in the pharynx, the train of events progresses by some immunological process which originates in the host and which cannot be interrupted by any therapeutic method yet devised.

The *immunological processes* which are involved in rheumatic fever and scarlet fever are not completely understood. There are, however, some clues which, when assembled, shed some-light on the problem and point the way for future study. Swift suggested that the synovial membranes and other tissues were sensitized during the silent period following the initial infection and then reacted somewhat like tissues respond after an injection of foreign protein (horse serum). Recent experimental studies by Rich and Gregory indicate that lesions resembling those in rheumatic carditis can result from anaphylactic hypersensitivity. More recent studies by Rich and clinical experience suggest that sensitization to the sulfonamides may cause widespread vascular lesions resembling those seen in periarteritis nodosa, lupus erythematosus, and rheumatic arteritis. Numerous workers have attempted to produce rheumatic fever and glomerulonephritis by repeated injections of streptococci or their products and other antigens and toxins, as well as foreign proteins including foreign serums. The lesions produced by foreign serum in rabbits may bear some resemblance to those of rheumatic fever. In experimental glomerulonephritis the most consistent results have been obtained by the use of specific antikidney serum. Masugi and others have demonstrated that chronic glomerulonephritis with its major clinical and pathological features can be produced by this method. The nephritis appears to be the direct result of the antigen-antibody reaction caused by the interaction of the antibodies of the antikidney serum on the antigen in the kidneys of the animal receiving the injection. It is remarkable that a single injection of antikidney serum is frequently sufficient to produce a progressive type of chronic nephritis terminating in death from renal insufficiency.

Attempts to reproduce cardiac lesions by injecting antiheart serum have met with little success although Masugi claims to have obtained foci of fibrinoid necrosis in the heart of rabbits injected with the serum of ducks

immunized with rabbit heart. Aschoff bodies, however, were not described. Bauer reported pulmonary lesions resembling rheumatic changes in rats injected with anti-rat heart serum from rabbits. Pericardial lesions were produced in some rats when the serum was injected into the pericardial sac. No lesions were described in the heart muscle. It has been demonstrated by Burkey, Schwentker and Comploier, and Hecht et al. that staphylococcus toxin when injected with specialized tissues of the rabbit, as lens, muscle, kidney and skin, renders these tissue substances antigenic and initiates formation of antibodies to them.

It was proposed by Cavelti, in our laboratory, that if glomerulonephritis can be produced only by specific antibodies for kidney the same mechanism might be operating in rheumatic fever. In the latter case the myocardium and connective tissues generally would become antigenic and lead to the formation of auto-antibodies. Since the hemolytic streptococcus was under chief consideration as the etiological agent, it was assumed that this organism participated somehow in initiating this immunological response in the production of auto-antibodies and resulting in cardiac and other lesions in situ. The studies by Cavelti to test the mechanisms concerned have been carried on over a period of years and only a brief summary of his reports can be given here. The general plan of the experiments was to inject animals (rats, rabbits) with emulsions of certain tissues from the same animal species in mixture with killed Group A, beta-hemolytic streptococci and subsequently to attempt to demonstrate, in the serum of these animals, antibodies reacting in vitro with saline extracts of the respective tissue emulsions. For controls, animals were injected with either tissue emulsion or streptococci alone. Kidney, heart muscle, skeletal muscle and connective tissue were chosen for tissue emulsions.

Serological studies were made using the collodion particle technic wherein the collodion particles sensitized with the antigen were agglutinated upon addition of serum containing homologous antibodies. By the use of this method it was found that after repeated injections of the mixture of tissue emulsion and streptococci, about half of the animals developed antibodies reacting in vitro with saline extracts of the plain homologous tissue. Animals injected with streptococci or tissue emulsion alone failed to show the formation of such antibodies. There appeared to be little or no cross sensitization to different tissues except in the group of heart, skeletal muscle, and connective tissue. It is of interest that these auto-antibodies showed a peak about seven to 10 days after each injection schedule, and tended thereafter to disappear rapidly from the blood stream, possibly due to absorption by the homologous antigens in the tissues.

It would thus appear that tissue emulsions in association with the hemolytic streptococcus are capable of reacting in some manner with homologous tissues in the living animal to render the tissues antigenic. Whether this combination is with normal tissue elements or those injured by some fraction or product of the growth of the streptococcus is not clear. In the



pathogenesis of a disease such as rheumatic fever it would be assumed that some toxin produced locally in the throat, or some compound produced at the portal of entry, is carried throughout the body affecting blood vessels in many tissues, making them antigenic. Studies by Cavelti on glomerulonephritis by this technic are more convincing than in rheumatic fever. However, in animals treated with emulsions of cardiac and connective tissue and streptococci, cardiac lesions were produced in a substantial number of animals. The commonest lesions produced were valvular endocarditis with inflammatory infiltration and proliferation. In many instances the majority of the cells were of the large basophilic type, occasionally multinuclear and arranged in a more or less nodular fashion. Slight degenerative changes were sometimes observed in the intercellular connective tissues. Proliferative changes were noted in the valves in some animals. In the myocardium *interstitial and perivascular changes* were less often seen than in the valves, and at times there was widespread scarring but nodule formation was not often seen. Less often pericarditis and arteritis, and peri-arteritis of large and medium-sized vessels, were noted. Mixtures of emulsions of skeletal muscle, relatively free of connective tissue and streptococci, failed to produce cardiac lesions, suggesting that connective tissue may be of greater importance in producing auto-antibodies than muscle tissue.

A search for auto-antibodies in the serum of patients with active rheumatic fever by Cavelti gave promise of success in a group of patients studied, using as antigen the saline extract of one normal human heart. These results could not be repeated. Whether the antigenic substance is unusually labile or the auto-antibodies are only transiently found in the blood in patients with the disease, or for other unknown reasons, could not be determined.

These studies suggest that the etiological agent, presumably the hemolytic streptococcus, by injury to, or in combination with, the connective tissues of the body produces auto-antibodies which act in vivo to bring about lesions in the living animal which may be progressive or may be reactivated by repeated exposure to the same organism. Whether we can carry the analogy over into clinical medicine and apply it to glomerulonephritis and rheumatic fever and other diseases cannot be assumed unequivocally at this time, but it presents the most promising lead we have.

#### SUMMARY

The pathogenesis of rheumatic fever is reviewed. The evidence that one or more strains of the beta-hemolytic streptococcus evoke a train of events leading to the clinical disease of rheumatic fever is convincing although not proved beyond question. The silent period following the initial symptoms in the pharynx suggests that some immune mechanism in the host is set in motion. Other immunological studies indicate that antibodies to the streptococcus are increased during this period. After the silent period the "trap is sprung" presumably by antigenic substances which are developed by the tissues of the host and perhaps are in the nature of auto-antibodies.

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## USE OF ESTROGENS IN MEDICINE\*

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ESTROGENS are substances which will provoke in numerous animal species the changes in tissues and in behavior which are known as estrus. Several steroids found in the adult female fit such a definition, the most potent being estradiol, from the metabolism of which are derived estrone and estriol. A variety of synthetic substances, not steroids, show similar estrogenic activities. The most widely known is diethylstilbestrol, and perhaps the most potent is dienestrol. Two great advantages of these synthetic compounds are their relatively lower cost and their slight loss of effectiveness when they are administered orally rather than parenterally. The disadvantage of synthetic materials is chiefly that a significant although small proportion of women receiving them report nausea or other unpleasant side-reactions, which are rarely noticed with the naturally occurring estrogens. Chemically altered natural estrogens have been prepared which share the advantage of high potency when taken orally. The commonest of these is ethinyl estradiol.

Natural estrogens may be secured from the graafian follicle liquor, from chorionic tissue, amniotic fluid, or most economically from the urine of pregnant mares. Crystalline pure single materials may be secured, although mixtures of several estrogens are known to be clinically effective. It is possible to use these natural estrogens either as free steroids, as the benzoate or propionate esters to delay absorption, or as the sodium salts of the estrogens conjugated with sulfuric or glycuronic acids, in which form they are found in urine.

The metabolism of estrogens is still known in only partial fashion. As described by Smith and Smith<sup>1</sup> estradiol is carried through a series of oxidative changes with formation of estrone and unidentified products which are no longer estrogenic. A small portion of the estrone is reduced to estriol. Only a small percentage of the estradiol can be recovered in urine in any of the estrogenically active forms. When progesterone is present, as during the third week of the menstrual cycle, or during pregnancy, the metabolic process is altered toward production of more estriol and less of the unidentified but estrogenically inactive products. These estrogenically inactive end-products are thought to stimulate the pituitary, which in turn stimulates the follicle to secrete more estradiol and also to ovulate and therefore to secrete progesterone. Under the influence of progesterone the alteration in metabolism of estradiol tends to reduced pituitary stimulation, thereby allowing decreased ovarian function and eventually menstruation. After progesterone secretion and activity have decreased, the original metabolic pathway

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for estradiol reappears, and the cycle is repeated. The Smiths report also that diethylstilbestrol acts in this regard like the estrogenically inactive products of estradiol, with potent stimulation of estrogen and progesterone production.

The biological effects of estrogens in women include the following:

1. Stimulation of myometrial growth
2. Stimulation of endometrial growth (tubular glands)
3. Stimulation of vaginal mucosal maturity
4. Stimulation of mammary duct growth
5. Stimulation of maturing changes in skin and its derivatives
6. Stimulation of secondary sex characteristics
7. Stimulation of union of epiphyses of long bones

In addition these steroids have some effects on salt and water balance, resembling the steroids of adrenal cortex origin. There are vasodilator effects of estrogens which may be important, even though not well understood. In addition to the effects upon the anterior pituitary already described it is known that large amounts of estrogens exert an inhibiting effect upon pituitary secretion, at least of the gonadotrophic hormones.

Diagnostic determination of estrogenic activity will include long term and short term effects. Over periods of months or years the best evidences of the action of estrogens are the presence of secondary sex characters, the proper timing of epiphyseal union, and the sustaining of regular menstrual rhythm or of fertility. These leave much to be desired in both quantitative features and in determination of the activity at a given time. For these latter needs the use of urine assays, chemical or biological, are not very helpful. Better information can be secured by use of the biopsy of endometrium<sup>2</sup> or the study of the exfoliated vaginal mucosal cells.<sup>3</sup> Recent evidence suggests that urethral cells may be at times an easily available substitute for vaginal cells.<sup>4</sup> The degree of progress from the small rounded cells of the deeper layers to the cornified and squamous cells of the outer layer of vaginal mucosa as seen in the material sloughing off spontaneously is the best of the semi-quantitative gauges of the intensity of estrogenic activity at any given time.

Therapeutic goals in use of estrogens may be the application of any one of the biological activities listed above. The most common is in the alleviation of the symptoms of the climacteric or menopause syndrome, in which field the experience with these preparations is greater than in all the others combined. The symptoms of the climacteric are most frequently due to a number of manifestations of autonomic nervous instability. In a few women this will resemble thyrotoxicosis sufficiently to constitute a problem in differential diagnosis. Exhibition of generous doses of any estrogen will produce symptomatic relief faster than can be achieved with iodine or with the antithyroid drugs. Frequently the climacteric syndrome has pronounced features of psychic distress, so that the diagnosis is an involutional syn-

drome. Endocrine therapy with estrogens is a most useful part of the program for the involution. Complaints about the joints are frequent, but the tissue changes involved are very poorly known. There may be some relationship to the early stages of osteo-arthritis. Estrogenic therapy in the early stages seems to afford not only subjective relief but also to restore normal outlines to the joint areas. Another type of osseous lesion seen late in the climacteric is osteoporosis.<sup>5</sup> This yields very slowly to use of estrogens.

Since several features of estrogen deficiency and the appropriate treatment belong essentially in the domain of gynecology, amenorrheas, menorrhagia, reduced fertility, vaginitis and kraurosis vulvae will not be discussed here. Dysmenorrhea is a problem faced by so many medical practitioners that it may be of interest to know that estrogens have been used with marked success in many cases of severe and recurrent pain. Hamblen and his associates<sup>6</sup> report that administration of generous doses daily from the fifth day of the flow for the next 20 days will eliminate the pain in most women. This is accompanied by suppression of ovulation and of secretion of progesterone. The benefits are purely temporary, as are any minor disturbances of the menstrual rhythm. Of course, fertility is reduced during such therapy. The cost of this treatment is not inconsiderable.

Occasionally there is failure to develop breast or uterine tissue during adolescence, and if the structures are not entirely lacking it may be possible to stimulate their growth by judicious and sustained therapy with estrogens. Exact procedures for this purpose are subject to clinical trial. It is suggested that estrogens should be administered in cycles, attempting to simulate the natural menstrual cycle of the ovaries, or if possible to supplement this cycle by careful timing of the doses.

Trials have been made with estrogenic therapy in control of acromegaly and of diabetes mellitus. These are based upon the inhibition of the anterior pituitary activity by large doses of estrogen. The success achieved is not striking. Synthetic estrogens may cause diabetes, at least in animals.<sup>7</sup> Use of estrogens to combat thyrotoxicosis has been reported, but is not dependable. Perhaps there is good reason to use these hormone materials in treatment of women with asthenic syndromes, provided there is evidence of deficient ovarian function in the patients. A quantitative diagnostic method is urgently needed before this type of therapy can be placed on an objective and sound basis. Empirical trials are safe if the physiological principles discussed above are kept in mind. Failures will be more frequent than successes, due in part to the many other causes of asthenia.

Estrogens may be administered via several routes: oral, parenteral, percutaneous, vaginal suppository, and subcutaneous pellet implantation methods being well known. The chief disadvantages of oral therapy are the requirement for larger doses than by the parenteral routes, and the risk of self-medication without professional advice. Oral therapy is nevertheless growing in favor as might be expected. Parenteral administration of

estrogens has usually been with solutions in vegetable oils, since the estrogens are so sparingly soluble in water that large doses could be administered only by repeated injection of large volumes. The oil solutions have been prepared with esters of estrogens which are slowly hydrolyzed and slowly absorbed, providing thereby a depot type of treatment, with benefits persisting from five to ten days after each dose. Since there are frequent unfavorable reactions to the introduction of such vegetable oils into muscle, the newer depot therapy is receiving favorable attention. This is based on either the pellet or the suspension of estrogen crystals in water. Pellets are absorbed slowly from their surfaces after having been placed in loose subcutaneous tissue spaces by small incisions or through trocars. Sometimes there have been local difficulties from foreign body reactions to these pellets. More recently the development of aqueous suspensions of very small crystals of certain estrogens has allowed the simple hypodermic injection of small volumes, following which the absorption of the crystals as they dissolve in tissue fluids provides sustained benefits for several days, comparable to use of oil solutions.

Vaginal suppositories were useful before the parenteral methods had been perfected, and continue to be helpful in treating vaginitis, where the local effect on vaginal mucosa is the important desideratum. This is now the case only in treatment of kraurosis or other atrophic conditions, under gynecological supervision.

Percutaneous administration of estrogens has had a curious history. When first proposed by manufacturers of cosmetic products it was resisted by medical men as being either futile or possibly a source of danger as a local carcinogen. It has been shown without any doubt that significant doses of estrogens can be absorbed through intact human skin, using either alcoholic solutions or ointments or creams. The fear of carcinogenesis has never been based upon authenticated cases, nor has all ground of fear been removed. Obviously the doses used would be of importance in this connection. The whole field of percutaneous administration of estrogens has had very little systematic study by qualified investigators. Systemic as well as local effects are involved. A recent review of the local activity of the sex hormones<sup>8</sup> presents little helpful information on this part of the problem, but points out the unfortunate exploitation of the public by purveyors of certain cosmetics. The remedy for such undesirable methods of treatment lies in careful study of the field by the medical profession.

Using any type of estrogen and any route of administration it is axiomatic that the doses must be made adequate by trial to achieve the therapeutic goal. Dosage needs almost always to be varied from time to time. This calls for professional judgment. Often large doses are required at first, and gradual reduction can be carried out without loss of control of the symptoms, as in the climacteric. Rather frequent and small doses are preferred to large doses at long intervals. The latter method tends to cause unduly rapid absorption of large amounts, with consequent temporary dis-

comfort, sometimes with exaggeration of menopausal tension states. If intervals between doses are too long, escape from control occurs, and the patient's lack of satisfaction is the result of the inadequate program.

Contraindications to use of estrogens come under several headings. Although it is probable that therapeutic doses of these hormones do not initiate the growth of carcinoma, it is possible that carcinomatous tissue of the genitalia or breasts may be made to grow faster in the presence of estrogens than without them. It is a matter of simple clinical caution to insist upon adequate physical examination before and at intervals during estrogenic therapy to make certain that no obvious malignancy is present. When there is malignant disease, or after carcinoma has been removed, it is considered unwise to use estrogens. Nevertheless there is recent evidence to suggest helpful treatment of certain types of breast cancer metastases in older women with these same substances.<sup>9</sup>

Endometriosis constitutes a contraindication to use of estrogens, since the symptoms are due to hyperplasia, secretion and bleeding from tissue which will atrophy only when estrogens are excluded, as by extirpation of ovaries. Other forms of treatment, such as with sedatives, cautious use of testosterone, or possibly with vitamin E, are available for women in the climacteric who have had endometriosis, as in carcinoma cases.

The other contraindications are quantitative, i.e. they are signals for reduced doses. Resumption of bleeding after the menopause suggests that the amount of estrogen employed is excessive. Menorrhagia in younger women has a similar significance. Of course, other causes of bleeding must be given consideration. Bothersome leukorrhea is more frequently a sign pointing in this same direction. Unwanted enlargement of the breasts and subjective tension states at times require reduction of dosage.

A word needs to be said for the woman whose symptoms require therapy with estrogens, but whose purse will not allow it. She still merits from her physician what he can and should do for her more fortunate sister who can purchase medication. With the rapidly expanded knowledge of the clinical significance of hormones, much of it has become available to our patients. Too often this is partial truth, and the consequence may be a mixture of unwarranted hopes and unnecessary fears. With his professional understanding of the problem the real physician will welcome the opportunity to present to each patient a simple explanation of her problem and of what he expects to do for her. There is no better way to achieve both gratitude and intelligent coöperation.

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# A NOTE ON CORONARY OCCLUSION AND MYOCARDIAL INFARCTION FOUND POST MORTEM AT THE MASSACHUSETTS GENERAL HOSPITAL DURING THE TWENTY YEAR PERIOD FROM 1926 TO 1945 INCLUSIVE \*

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HEART disease as a cause of death in this country today far exceeds all other causes. Coronary heart disease is one of the three most common types of cardiac involvement. Since this is so and since coronary occlusion and myocardial infarction are prone to involve in particular the leading citizens in every community, coronary heart disease has become a (perhaps *the*) most vital health problem that demands our attention. Its etiology is of prime importance and is now the subject of an extensive long range research at the Massachusetts General Hospital. In the course of preparing a background for our current and future studies, we have analyzed the post mortem records of this hospital over a period of 20 years. The results of this analysis we are briefly presenting herewith because of their interest and value as the experience of a large clinic concerned of late years with many cases of heart disease. The tables which summarize the data speak quite clearly for themselves and demand only brief comment and discussion. This report deals with the pathological findings per se. We have not included clinical or electrocardiographic correlations.

## INCIDENCE

A glance at table 1 demonstrates the fact that less than 25 years ago not only the practicing physician but even the pathologist himself was overlooking coronary heart disease, which certainly did not begin out of the blue 20 years ago and expand in its incidence in such a rapid degree. Even now it is easy occasionally to miss either coronary occlusion or myocardial infarction at autopsy. However, it is also probable that we do have under our care in the wards nowadays more cases with coronary heart disease than we had 20 years ago when they might have been treated at home or even overlooked altogether.

## SITE OF CORONARY OCCLUSION

It will be seen (table 2) that the anterior descending branch of the left coronary artery is by far the choice as a site for thrombus formation over all other sites in both acute and chronic cases, with the right coronary a poor

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TABLE I

Incidence of Autopsy Diagnosis of Coronary Thrombosis and Myocardial Infarction  
at the Massachusetts General Hospital  
1926-1945 Inclusive

Year	No. of Autopsies	No. of Cor. Throm. and Myo. Infarct.	%	Year	No. of Autopsies	No. of Cor. Throm. and Myo. Infarct.	%
1926	170	0	0	1936	370	27	7.3
1927	167	4	2.4	1937	446	27	6.0
1928	220	9	4.1	1938	332	26	7.8
1929	225	7	3.1	1939	361	34	9.4
1930	299	9	3.0	1940	406	55	13.4
1931	371	23	6.2	1941	419	59	14.1
1932	374	17	4.8	1942	390	32	8.0
1933	394	27	6.9	1943	439	55	12.5
1934	420	29	6.9	1944	405	44	10.8
1935	436	21	4.8	1945	374	25	6.7

TABLE II

Distribution of Coronary Occlusions at the Massachusetts General Hospital  
1926-1945 Inclusive

Arteries	Left Main	Anterior Descending	Left Circumflex	Ant. Desc. and Left Circumflex	Right	Right and Left	Total
Acute	16	127	36	3	78	19	279
Healed	18	161	45	36	29	54	343

second. In a moderate number of cases there were multiple sites, and quite a few of the fresh right coronary occlusions were found in cases with the left coronary already blocked, a condition which affords little chance for survival. The great majority of all these cases showed marked atherosclerosis of the coronary arterial tree, although there were some striking exceptions.

#### SITE OF MYOCARDIAL INFARCTION

The anterior wall of the left ventricle supplied by the descending branch of the left coronary artery was much the most common location of infarction (table 3), being almost twice as common as the posterior site, while lesions limited to the septum or right ventricle were quite infrequent. However, in 72 of the 190 hearts with fresh anterior myocardial infarction there was an

TABLE III

Site of Myocardial Infarctions at the Massachusetts General Hospital  
1926-1945 Inclusive

Infarction	Total	Anterior	Posterior	Septal	Rt. Vent.	Ant. and Posterior	Recent and Healed
Recent	267	190	109	5	8	45	74
Healed	289	222	122	5	2	62	

extension into the adjacent portion of the septum, which was also true in 35 of the 109 hearts with fresh posterior infarcts. The size of the infarcts varied from 0.3 cm. by 0.1 cm. to 12 cm. by 15 cm. In many cases the lesion involved the entire thickness of the wall but sometimes extended only half or three quarters of the distance.

#### ASSOCIATION OF CORONARY OCCLUSION AND MYOCARDIAL INFARCTION

Table 4 clearly shows that coronary occlusion and myocardial infarction are not synonymous, as was once thought, and as is still often unfortunately implied in diagnostic terminology. In fact only half of the cases of recent coronary occlusion showed infarcts. The classical work of Schlesinger and

TABLE IV  
Association of Coronary Thrombosis and Myocardial Infarction  
at the Massachusetts General Hospital  
1926-1945 Inclusive

Myocardial Infarction			Coronary Thrombosis		
Total Recent	Associated with Cor. Occl.	Unassociated with Cor. Occl.	Total Recent	Resulted in Myo. Infarct.	Not Resulted in Myo. Infarct.
267	162 (60.6%)	105 (39.4%)	261	131 (50%)	130 (50%)

Blumgart clarified this discrepancy for us years ago. Also as these authorities noted there may be a lack of correlation between the site of the acute occlusion and the site of the infarct due to previous occlusions and the development of a collateral circulation. Thus in our series there were 12 cases with fresh anterior myocardial infarcts and acute occlusion of the right coronary artery in 11 and of the left circumflex in the remaining one with old occlusion of the left anterior descending artery.

#### CARDIAC ANEURYSMS AND RUPTURES

Large cardiac aneurysms due to myocardial infarction we found in 10 per cent of cases (table 5) although aneurysmal concavities of small degree with shallow depression are commonly present. Both large and small aneurysms are likely to be the site of mural thrombi. Rupture of the ven-

TABLE V  
Cardiac Aneurysms and Ruptures at the Massachusetts General Hospital  
1926-1945 Inclusive

Kind	Total No.	Anterior		Posterior	Septal
Aneurysm	52	38		11	3
Rupture	23	Lt. 21	Rt. 1	0	1

tricular wall at the site of an acute myocardial infarct occurred in less than 5 per cent of all these coronary cases. Both aneurysms and ruptures were preponderantly in the anterior wall of the left ventricle. In one case involving the septum, a ventricular septal defect resulted.

### MURAL THROMBOSIS WITH MYOCARDIAL INFARCTION

We do not always appreciate how commonly thrombosis occurs within the ventricular cavity, mostly the left, and elsewhere as well as over the site of acute infarcts (table 6). Since such thrombi are often the cause of peripheral arterial embolism a strong argument exists for the use of anti-coagulants early in the course of the acute illness.

TABLE VI  
Association of Mural Thrombi and Myocardial Infarction  
at the Massachusetts General Hospital  
1926-1945 Inclusive

Myo. Infarct. Recent and Healed	No. of Cases with Mural Thrombi	Mur. Throm. with Myo. Infarct.	Fresh Throm. with Acute Myo. Infarct.	Organized Throm. with Healed Myo. Infarct.	Unassociated with Myo. Infarct.
489	232	175 (32.7%)	112 (41.0%)	58 (26.1%)	43

### SYSTEMIC ARTERIAL EMBOLISM

Of the 207 cases with thrombi in the left heart chambers (table 7), 95, almost half, had complicating embolism of the cerebral, renal, splenic, or limb

TABLE VII  
Association of Mural Thrombi and Arterial Embolism at the Massachusetts General Hospital  
1926-1945 Inclusive

Total Thrombi in Lt. Heart	No. of Cases with Art. Emb.	Art. Embol. with Thrombi in Left Heart	Art. Embol. without Thrombi in Left Heart
207	153	95	58

arteries or even of the aorta itself. There were half as many cases again with peripheral arterial block who showed no such thrombi in the left heart itself; evidently the embolus constituted the entire thrombus.

### PULMONARY ARTERIAL EMBOLISM

We have come to know well the frequency and seriousness of pulmonary embolism (table 8) as a complication of acute myocardial infarction and to realize that such embolism has its origin rarely from intracardiac thrombosis but almost invariably from an often unrecognized leg vein thrombosis. This helps to explain the discrepancy between the 106 cases of pulmonary embolism in the present series and the 36 cases of that condition which showed

TABLE VIII

Association of Pulmonary Infarction and Myocardial Infarction  
at the Massachusetts General Hospital  
1926-1945 Inclusive

Total Pul. Infarct.	With Rec. Myo. Infarct.	With Healed Myo. Infarct.	With Recent Ant. Myo. Inf.	With Recent Post. Myo. Inf.	No. Throm. in Rt. Heart
106	60 (20.9%)	46 (20.7%)	29 (15.3%)	31 (28.4%)	49 (36 with pul. inf. 13 without pul. inf.)

thrombi in the right heart chambers. Even in this latter group the leg veins rather than the heart were probably the site of the offending thrombi. Until recent years, however, the leg veins have not been investigated in such cases post mortem.

#### PERICARDITIS COMPLICATING MYOCARDIAL INFARCTION

The pericarditis (table 9) found with either acute or healed myocardial infarction was never serious per se and usually only slight to moderate in degree. It occurred in about a third of the acute and a quarter of the chronic cases. Quite possibly it had left little or no trace in some of the healed cases.

TABLE IX

Association of Myocardial Infarction and Pericarditis  
at the Massachusetts General Hospital  
1926-1945 Inclusive

Recent Myo. Infarct.	Acute Pericarditis	Healed Myo. Infarct.	Pericardial Adhesions
267	92 (34%)	222	61 (27.5%)

#### PROGNOSIS

This postmortem analysis affords little information as to prognosis in coronary occlusion or myocardial infarction. There were, however, more cases in this 20 year period with healed or chronic lesions of both categories than with acute (tables 2 and 3); not infrequently, though in a minority of cases, acute coronary occlusion or myocardial infarction was superimposed on the hearts with chronic or healed scars but more often there was but the one process, fresh or old. Some other disease was responsible for death in not a few of the chronic cases. So far as the relative prognosis according to site of the lesion was concerned there was little to choose, though anterior myocardial infarcts seemed to be slightly more likely to lead to rapid death. In the total series there were 84 cases that died within a few seconds to a few hours of the acute heart attack which not infrequently occurred itself unexpectedly on the ward in the hospital. Of these 84 cases, 35 showed fresh anterior myocardial infarcts, 15 fresh posterior infarcts, and 34 acute coronary occlusion without infarction, 18 of which involved the left coronary

artery and 16 the right. Of another 108 cases who died of their acute heart disease within a few days but survived the first few hours, 51 showed anterior infarcts, 26 posterior, 20 both anterior and posterior, six right ventricular alone, and five septal alone. It is to be remembered that anterior myocardial infarcts exceeded in number posterior infarcts in the total series, both in the acute and in the chronic stages, 190 to 109 in the case of the acute and 222 to 122 among those healed. Despite that fact, however, the somewhat greater seriousness of the anterior infarcts was borne out particularly by the incidence of cardiac rupture which occurred in 22 cases of anterior infarcts, 1 case of septal infarct, and in no case of posterior infarct.

### CONCLUSION

An analysis of the post mortem records at the Massachusetts General Hospital over a period of 20 years (7,018 cases) has revealed an increasing incidence of the diagnosis of coronary occlusion and myocardial infarction from a very low figure in 1926 to percentages of 13 to 14 in 1940 and 1941; a change to be attributed in part at least to a more active search for these lesions. Occlusion of the left coronary artery, involving preponderantly the anterior descending branch, was much more common, especially in the chronic stage, than occlusion of the right coronary. Anterior myocardial infarcts, both recent and healed, were nearly twice as common as posterior myocardial infarcts; not infrequently one was superimposed on the other, i.e. a fresh lesion in a heart with an old scar. The anterior myocardial infarcts were somewhat more serious than the posterior; this was particularly shown in the case of ruptures of the heart which occurred through the *anterior* wall in 22 of the 23 cases. Coronary occlusion and myocardial infarction did not always coincide and should not be considered as synonymous.

# EFFECT OF INTRAVENOUSLY ADMINISTERED OXYGEN ON SYMPTOMS AND VITAL CAPACITY IN BRONCHIAL ASTHMA \*

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GASEOUS oxygen has long been administered intravenously to animals without deleterious effects.<sup>1</sup> Attempts have been made sporadically over many years to utilize the intravenous route for the administration of oxygen in cases of anoxia in man.<sup>2</sup> These attempts were not continued further because of the development of such undesirable effects as embolism or cardiac tamponade. An analysis of these attempts shows that the amounts of oxygen administered were too large or that the gas was injected too rapidly or at too high a pressure. Ziegler,<sup>3</sup> in 1941, described an apparatus for administering pure (commercial 100 per cent) oxygen intravenously at low pressures and in physiologic amounts, and mentioned its use by this route for several patients with various forms of anoxemia. He noted no deleterious effects, but gave no details of diagnosis or results.

During the previous investigation by some of us of the effects of intravenously administered 100 per cent (commercial) oxygen in experimental shock in animals, and in three cases of severe acute progressive (secondary traumatic) shock in human beings,<sup>4</sup> occasion arose to study the effects of oxygen so administered, on the vital capacities of a group of patients suffering from severe, long-standing bronchial asthma of the perennial type. All the patients in this study gave histories of long-standing, frequently recurring asthmatic attacks; all were experiencing a diminishing response to bronchodilators during the attacks; all showed markedly diminished vital capacities when tested during attack-free intervals, a finding at variance with that of Feinberg.<sup>5</sup> As pointed out by Westcott and Gillson,<sup>6</sup> vital capacities are diminished in long-standing bronchial asthmatics, even during intervals between attacks.

As a corollary to the above studies, we attempted to correlate the frequency and severity of the asthmatic attacks with the vital capacity levels, such levels being determined at periodic intervals following the intravenous oxygen therapy. It had previously been shown by Westcott and Gillson<sup>6</sup> that the increase in vital capacity obtained in that study by means of exercises, postural drainage and epinephrine inhalation therapy was associated

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with symptomatic improvement for periods up to nine months; and that the greatest degree of improvement occurred in those cases initially showing the greatest diminution in vital capacity. From a reading of their paper, it appears that the prescribed exercises and inhalation therapy were continued throughout the period of study. In our cases, intravenous oxygen was administered in single or divided doses during one period of hospitalization and was not thereafter repeated while under subsequent clinical observation.

All our patients showed evidences of stagnant and anoxic anoxia. The latter is found in true bronchial asthma, and is due to the incomplete saturation of the blood leaving the lungs which may be observed in any form of respiratory depression. The former is also encountered in bronchial asthma, and is often an important factor when poor cardiac function, with decreased blood volume and delayed pulmonary circulation time, is superadded.<sup>7</sup> Anoxic anoxia was of importance in cases 5, 6 and 7 of this series. No cases of anemic anoxia were encountered.

It has been shown in cases of shock that a change from a 95 per cent oxygen—5 per cent carbon dioxide inhalant mixture to a 100 per cent oxygen inhalant causes a marked rise in oxygen partial pressure (from 14 to 21 mm.), with a 50 per cent rise in oxygen availability to the body tissues.<sup>8</sup> In asthmatic attacks the alveolar ventilation is usually poor to a considerable degree, due to the muscle spasm of the bronchioles and to the frequently present intrabronchial and intra-alveolar exudation. That pulmonary exudates may actually be interstitial, and not demonstrable as clinical edema with râles, was pointed out by Drinker<sup>9</sup>; they may, however, effectively impede the transport of oxygen to the pulmonary alveolar capillaries. This can be realized at a glance, when it is noted that the diffusion coefficient of oxygen through the pulmonary epithelium of the intact animal (i.e., the number of cubic centimeters absorbed per minute per millimeter of mean pressure difference between the the blood and alveolar air) varies between 23 and 45, while the diffusion coefficient for oxygen through water (at body temperature) is 0.51.<sup>10</sup> It is for this reason that it was deemed advisable to attempt to by-pass a functionally deficient lung by means of the intravenous administration of oxygen.

As pointed out in our previous communication,<sup>4</sup> there is no danger of air-embolism or vapor lock if the intravenous administration of oxygen is carefully regulated and kept within physiologic volume, pressure and flow-rate. It may again further be emphasized that pure oxygen is utterly dissimilar from air; the former is entirely respirable; the latter, i.e. air, is low in oxygen content (20.94 volume per cent) and is composed almost wholly of irrespirable gases (79.02 volume per cent of nitrogen and other inert gases). Finally, though air-embolism is the perpetual *bête-noir* of medicine, it is, in actual experience, as pointed out in our previous paper, a rarity.

## METHOD OF STUDY

Eight of nine patients with severe long-standing perennial asthma were selected from the clinic, where they had been observed for a number of years; one was admitted to the clinic after participating in this study. The records of these patients indicated that their asthmatic attacks had been increasing in frequency and severity and that the usual forms of therapy had become ineffectual. At the time this study was begun, each patient had been having repeated asthmatic attacks daily for a prolonged period of time. Some were skin sensitive, others skin negative on test. Upon admission to the hospital, vital capacity determinations,\* in duplicate, were made when the patient was in a free interval. In cases 5, 6 and 7, electrocardiograms were taken prior to the administration of oxygen. Blood counts, taken on all patients, showed no abnormal findings. In particular, there was no anemia.

When two successive vital capacity determinations showed figures in agreement to 2 per cent, the oxygen administration was begun. Using the Ziegler technic and apparatus,<sup>3</sup> 100 per cent (commercial) oxygen was administered intravenously at a rate of 600 c.c. per hour, and at a pressure just sufficient to clear the glass viewing tube, proximal to the intravenous needle, of the blood that had refluxed into it upon venipuncture, i.e., a pressure just above venous pressure. The intravenous oxygen was allowed to flow for periods of from two to 17 hours without interruption, except when it became necessary to clear the needle of the occasional clot that formed. In two cases (1 and 8) a single course of intravenous oxygen was administered. In three cases two courses were administered (case 3: 17 and four hours; case 4: 15 and 10 hours; case 7: 12 and 12 hours). In three cases three courses were administered (case 2: 15, six and two hours; case 6: 14, 14 and 10 hours; case 5, five, two and four hours). Vital capacities were again determined, with the patient not in an attack, on the day after the oxygen was discontinued or upon discharge from the hospital. In the cases in which the oxygen was administered in divided doses, vital capacity determinations were performed just before each administration. In cases in which asthmatic attacks occurred during the period of study in the hospital, at least four hours, in which the patient was symptom-free, were allowed to elapse before vital capacity determinations were performed.

After the oxygen was finally discontinued, the patients were discharged, to be followed up in the clinic. A daily record of the number and severity of attacks was kept. Vital capacity determinations, all again during an attack-free state, were made at intervals during the succeeding year. After discharge from the hospital, some of these patients did not return to the clinic for periods of from two to four weeks, and in this period they received no other form of therapy.

\*The McKesson water spirometer was used in these determinations.

## CASE REPORTS

*Case 1.* D. G., age 45, housewife, was admitted to the allergy clinic September 1940 with a history of perennial attacks of bronchial asthma of 20 years' duration associated with fall hay fever and a fall aggravation of the asthmatic attacks. Since 1939 the attacks had become more frequent and severe.

Examination revealed an obese, white female, weighing 224 pounds, with a typical asthmatic chest, infected tonsils, and a blood pressure of 156 mm. Hg systolic and 90 mm. diastolic. Roentgenogram of the lungs was negative; roentgenogram of the sinuses showed a membranous thickening of ethmoids and maxillary antra. Nasal examination did not reveal clinical evidence of sinusitis. The blood smear showed 8 per cent eosinophiles. On test, she showed positive reactions to ragweed, dust and kapok and a marked reaction to silk which test was followed by a constitutional reaction controlled with adrenalin.

Specific therapy was begun in January 1941 with ragweed and dust extracts and an autogenous vaccine, and was continued regularly up to her admission to the hospital with moderate improvement but without freedom from symptoms at any time. Exacerbations occurred during the summer and fall months. Prior to admission to the hospital on October 5, 1942 she had had daily recurring attacks of asthma during August and September so persistent that, as she stated, "I was afraid to go to bed." These attacks were still present at the time of her admission to the hospital. The vital capacity determination on October 6, 1942 was 1,600 c.c.

Intravenous oxygen was begun at 11:00 a.m. on October, 6, while asymptomatic, and was given continuously for 14 hours. Prior to this, the patient always complained of coldness of the extremities. Immediately after the beginning of intravenous oxygen she felt a flushing and warmth of the left side of her body (left arm injected) and two hours later the right side felt warm, while the left side of her body cooled off. During this therapy she developed a mild wheezing spell that lasted five minutes. In all, she received 8,000 c.c. of intravenous oxygen in 14 hours. She was discharged from the hospital October 7, 1942. The vital capacity determination on October 7 was 2,100 c.c., an increase of 500 c.c., or 31 per cent over pretreatment level.

On October 15, 1942 she returned to the clinic and reported that she had been free of asthma except for one five minute attack after going through the contents of an old trunk. She felt definitely improved, was free of nocturnal attacks although coughing, and now was able to walk without symptoms, although previously the mere walking from one room to another resulted in difficult breathing and wheezing. She stated that she breathed more deeply and more freely now and that the act of talking was no longer associated with a choking sensation and tightness in her throat. Subsequent vital capacity studies showed the following:

October 28, 1942:	2,100 c.c.
November 4, 1942:	2,100 c.c.
February 3, 1943:	1,700 c.c.
March 29, 1943:	1,500 c.c.

During this six month period she continued to attend the clinic regularly, receiving specific therapy. In that time she had one attack of asthma and an occasional mild wheezing spell. Although this apparent improvement coincided with the termination of the fall hay fever season, such improvement had not occurred in previous years at a similar time. Since this therapy there has been a decided improvement in her case up to the present time. The coseasonal asthmatic symptoms have now been reduced to a mild wheeze, and the perennial nasal symptoms have practically disappeared. In all, she received 8,000 c.c. of oxygen in one period of 14 hours with a

maximal increase in vital capacity of 500 c.c., or 31 per cent, which was maintained for a period of one month and this slowly diminished to pretreatment level after five months.

*Case 2.* B. R., age 18, hospital employee, was admitted to the allergy clinic June 7, 1941 with a history of hay fever from August to October of 1938 and with a recurrence of symptoms during December of 1938. In 1939 she had had similar symptoms from August to October with a similar recurrence in December of the same year. In 1940 hay fever symptoms appeared from April to June and from August to October. Asthmatic attacks occurred during these periods, requiring adrenalin injections by an ambulance physician on several occasions. Prior to admission to the clinic in June 1941 she had had frequent severe asthmatic attacks complicating her hay fever. There was a history of frequent upper respiratory infections. She had had infantile eczema. The familial history included hay fever in her mother, asthma in her paternal grandfather, hay fever in two maternal uncles, one aunt and one first cousin, and one paternal first cousin. Her blood count was normal.

On test, she was sensitive to the pollen of ragweed, grasses and trees, to dust, cat and dog epithelium, horse serum and feathers. There were slight and moderate reactions to a variety of foods which were thereupon eliminated from the diet. Roentgenogram of the sinuses revealed clouding of the ethmoids and sphenoids and veiling towards the floor of both maxillary antra. Roentgenogram of the lungs was negative. Frequent nasal examinations revealed the presence of a purulent paranasal pansinusitis.

During the first year treatment at the clinic with specific therapy and local nasal therapy resulted in no improvement in either the hay fever or asthmatic symptoms. She was admitted to the hospital on October 12, 1942 after having had daily recurring attacks of bronchial asthma for two months. Her description of the symptoms revealed that she went to bed feeling well and invariably an asthmatic spasm occurred within two to three hours. The vital capacity determination on admission was 2,100 c.c.

After three hours in bed, a severe attack developed. Intravenous oxygen was begun at 5:40 p.m. Within five minutes she reported that the difficult breathing had ceased, although on auscultation wheezing respirations were still audible. Before the oxygen was started, her entire body felt cold but within five minutes this passed into a feeling of general body warmth. After one hour of oxygen therapy, labored breathing again appeared and the needle was found to be clogged. After the intravenous oxygen flow was reinstituted, the dyspnea immediately again disappeared. After two hours, although the wheezing respiration was still present on auscultation, she was comfortable and there were no subjective signs of asthma. At one point, when the pressure of the flow of oxygen accidentally became too great, she felt choked and dizzy but this passed when the pressure of the flowing oxygen was reduced. At 9:00 p.m. she was resting comfortably, although occasionally wheezing and coughing, but she did not appear to be in an asthmatic attack. After eight hours, the oxygen was discontinued. On the following day, October 13, she felt exceptionally well, remarking after the vital capacity was taken that, "I can now take a deeper breath than I can remember." The vital capacity determination on October 13, 1942 was 2,500 c.c. as compared with the initial reading of 2,100 c.c.

At 7:00 p.m. that day she developed another severe attack of asthma while talking to a visitor. At 7:30 p.m. oxygen was started intravenously and within five minutes there was relief of the dyspnea although wheezing could be heard. She experienced a feeling of warmth over the entire body which persisted as long as the oxygen flowed. At 9:10 p.m. the oxygen was discontinued when the patient appeared to be comfortable. She slept well until 6:00 a.m. on October 14, when another severe attack occurred. Intravenous oxygen was started at 6:30 a.m. producing bodily warmth within five minutes and relief of dyspnea within 30 minutes. Oxygen was discon-

tinued at 10:000 a.m. The vital capacity determination on October 14, 1942 was 2,400 c.c.

During the remainder of that day and the following night the patient was comfortable. On October 15, 1942 a mild attack of asthma was relieved by five minims of adrenalin. The vital capacity determination on the day of her discharge from the hospital, October 15, 1942, was 2,800 c.c. In the following two weeks she was asthma-free for the first time in three months although still coughing. Subsequent vital capacity studies showed the following:

October 17, 1942:	2,800 c.c.
October 28, 1942:	2,800 c.c.
November 4, 1942:	2,800 c.c.
February 3, 1943:	2,200 c.c.
June 1, 1943:	1,300 c.c.

On October 28 and 29, 13 and 14 days after her discharge from the hospital, she had two mild wheezing spells in the early morning hours lasting about 20 minutes. On December 2, 1942 she had an attack of asthma while walking in a heavy wind. Since then, and up to June 1, 1943, she attended the clinic regularly, continued to receive specific therapy and had an occasional cold and sore throat but no asthmatic attacks except on May 28, 1943 following the ingestion of fish. During the hay fever seasons of 1943 and 1944 she was asthma-free although she coughed and had an occasional wheeze.

In all she received 11,500 c.c. of oxygen during a two day interval which was divided into periods of 15, six and two hours each. There was an increase in vital capacity of 700 c.c., or 33 per cent, which slowly diminished to pretreatment level within four months and then further diminished beyond that in nine months.

*Case 3.* K. B., housewife, was admitted to the allergy clinic on July 29, 1937 at the age of 29 complaining of perennial attacks of shortness of breath, wheezing and choking since the age of 27. At first these attacks were infrequent, generally preceded by colds and worse in winter months. In the two months preceding her admission to the clinic, the attacks occurred daily. The personal and family history was negative. There were no hay fever symptoms.

Examination revealed poor teeth, inflamed gums and a red and inflamed throat. The heart was negative. There were many sibilant and sonorous râles in both lungs. The blood pressure was 125 mm. Hg systolic and 80 mm. diastolic. On test she reacted moderately to dust, feathers, kapok and orris root. There were only slight reactions on test and retest to plantain and ragweed. The roentgenogram of the chest was negative; roentgenogram of the teeth showed retained root fragments, an apical abscess of the left lower bicuspid and a rarefaction about the roots of the left upper cuspid. The nasal examination revealed polypoid degeneration of both midturbinates. On roentgenogram, both ethmoids were cloudy, especially the right. The Wassermann reaction was negative. A blood count showed hemoglobin 14.8 gm., red blood cells 4,100,000, white blood cells 6,000 with 2 per cent eosinophiles.

She was treated with food and inhalant elimination and substitutions and hypo-sensitized with extracts of dust and feathers. She also received stock vaccine as well as local nasal treatment. After five infected teeth were extracted she improved until the fall of 1938. As a result of an aggravation of clinical symptoms during the ragweed season, ragweed injections were added to the treatment in spite of only slightly positive skin sensitivity. The following year, with exacerbation during the grass season, retests remained negative to timothy but moderate with itching to plantain, and plantain injections were added to her treatments. In spite of high ragweed dosage during 1939, there was little improvement in her symptoms during that year.

These symptoms continued through the winter of 1939 and the early part of 1940. On retest, positive reactions to timothy appeared for the first time and this was then added to her treatment. During this period, she was under observation and treatment by the otolaryngologist but little evidence of infection was found although polypoid degeneration of the mid-turbinates persisted. She continued moderately asthmatic with a persistent cough through 1941 and, in spite of pollen therapy, there was no relief during the pollen seasons. Some attacks could be traced to specific food sensitivity, especially fish and nuts. Toward the end of 1941 she began to show moderate reactions to various trees and in the spring of 1942 showed a marked reaction on test to timothy in weak concentrations. She was somewhat improved in the first half of 1942 but thereafter her asthma gradually became more severe and persistent. Examination failed to reveal active infection in the sinuses. She was admitted to the hospital October 16, 1942 having had daily recurring severe attacks of bronchial asthma since August. The vital capacity determination on admission was 800 c.c.

On October 17 and 18 she was comfortable with barbiturates and rest in bed, although she wheezed and had slight difficulty in breathing for which she did not require adrenalin. On October 19 at 6:45 a.m. she received a small dose of adrenalin for the relief of a mild asthmatic attack. At 5:00 p.m. on the same day, the asthma became more pronounced and intravenous oxygen was started. In 15 minutes she was relieved, after feeling warm all over her body and perspiring freely. Oxygen was continued throughout the night and was discontinued at 9:00 a.m. on October 20, 1942, after 17 hours, at which time she stated that her lungs felt clear and that she could breathe easily and freely. During that night she slept intermittently. The vital capacity determination on October 20, 1942 was 1,200 c.c., an increase of 400 c.c. On October 20 at 8:00 p.m. oxygen was again started and discontinued at 12:30 a.m. on October 21, after four hours. During this period she slept and was fairly comfortable. The vital capacity determination on October 21, 1942 was 1,500 c.c., an increase of 700 c.c. over the initial reading. She continued comfortable during the day and night of October 21 and was discharged from the hospital on October 22 at noon. She remained symptom-free for four days until October 26, 1942 when mild wheezing began and this continued until October 31, 1942. This was attributed to the ingestion of fish on two occasions during that week, contrary to instructions. Subsequent vital capacity studies showed the following:

November 4, 1942: 1,400 c.c.

February 3, 1943: 1,200 c.c.

May 23, 1943: 1,000 c.c.

On January 7, 1943 she reported that she had contracted a cold, precipitating a severe asthmatic attack which responded promptly to sulfa therapy. A discharging ear which complicated this infection did not respond to sulfa therapy. On April 1, 1943 she reported a mild asthmatic spell following another upper respiratory infection.

In all she received 9,000 c.c. of oxygen in two periods of 17 and four hours respectively, with an increase in vital capacity of 700 c.c., or 87 per cent. This increase was maintained for two weeks and fell to a level of 25 per cent above the pretreatment vital capacity at the end of six months.

*Case 4.* B. M., age 45, printer for 20 years, was admitted to the clinic on August 1, 1940 with a history of severe and persistent attacks of bronchial asthma since January 1940. During his initial attack, he was admitted to a county hospital where nasal surgery was performed for an infection of the sinuses and a deviation of the septum. Following this, he improved until May 1940 when nightly attacks recurred, relieved by adrenalin injections. During July, the month prior to his admission to the clinic, he had two or more attacks of asthma nightly. The family history was negative for allergy.

Examination revealed hypertrophied and diseased tonsils. Nasal examination revealed a bilateral purulent discharge in both ethmoid and sphenoid areas. Transillumination of the sinuses showed an absence of aeration of both antra and of the left frontal sinus. Antral washes yielded large flakes of pus from the right side; the left was negative. Roentgenographic examination showed a veiling of the left frontal sinus and both ethmoid and maxillary sinuses. A diagnosis of paranasal sinus infection was made. The heart was negative. Many sonorous râles were heard throughout both lungs. Skin tests were essentially negative except for a moderate reaction to dust and feathers. The blood count showed hemoglobin 12 gm., red blood cells 3,990,000, white blood cells 5,000 with 4 per cent eosinophiles. Urinalysis was negative.

During the following year he received local nasal treatments, refusing further surgical intervention because of the apparent failure of previous surgery to give lasting relief. Hyposensitization with dust extract and injections of a stock catarrhal vaccine did not afford any relief from his attacks. His attacks became more severe and more frequent. He obtained moderate relief for about two hours with adrenalin injections during these attacks. From May 1941 to September 1941, he received a course of caffeine sodium benzoate injections, at first daily and then twice weekly with fairly good results, but this was discontinued because of his extreme nervousness and apprehension. Following the cessation of this therapy, he had three to four attacks of asthma daily. During the month of October 1941 he was bedridden and required adrenalin injections daily by the ambulance surgeon for relief. Following surgery for acute appendicitis in 1941, his attacks became milder and less frequent. In December 1941 and in January 1942, he spent eight weeks in bed with further severe asthmatic attacks of varying intensity and duration, requiring one to two adrenalin injections daily. The regimen, consisting of iodides by mouth, adrenalin by inhalation, local nasal therapy and injections of dust and vaccine, yielded very little relief. Dietary control was carefully observed. From March to October 1942 there was no apparent improvement in either the severity or the frequency of his asthmatic attacks. Pollen retests remained negative. Oral nicotinic acid at first eased the attacks, but this effect was soon lost. Repeated nasal examinations still revealed the presence of bilateral ethmoiditis. He was admitted to the hospital on October 27 at 1:00 p.m. in a mild asthmatic attack. The vital capacity determination on admission, before instituting treatment, was 2,200 c.c.

On October 28 a severe attack of asthma was reported at 7:00 p.m. Intravenous oxygen was started immediately and was continued until 10:00 a.m. on October 29. In one-half hour he felt a warmth over his entire body, especially the back of his chest, and the attack of asthma was relieved in two hours. He slept through the night while under the intravenous therapy. During the next 12 hours he reported that he felt very well. The vital capacity determination on October 29, 1942, during an asymptomatic period, was 2,700 c.c., an increase of 500 c.c. or 23 per cent over the pretreatment level.

On October 29, at 10:00 p.m., he again developed an asthmatic attack. Intravenous oxygen was started at 10:30 p.m., and was continued until 10:00 a.m. the following morning, October 30. Within 15 minutes after the oxygen therapy was begun, he developed a warmth of the body and a total cessation of the asthmatic symptoms. He slept throughout the night while receiving oxygen therapy. The vital capacity determination on October 30, 1942 was 3,200 c.c., a further increase of 500 c.c. with a total increase of 46 per cent over the pretreatment level. He felt very well that day, was free from symptoms the following night, and was discharged from the hospital the morning of October 31, 1942.

Following his discharge, he had two mild asthmatic spells on two days during the first week and none in the following two weeks. He felt well enough during this

period to try out the effects of physical exercise on his symptoms, since he previously could not walk more than five blocks without developing dyspnea and wheezing. Now he was able to walk 25 blocks before he noticed shortness of breath or wheezing. This mild attack lasted but 30 minutes and subsided. He was asthma-free for the first time without ephedrine or adrenalin medication although he still coughed and had spells of wheezing. The feeling of oppression of his chest was gone and he felt that he was breathing more easily and deeply. Subsequent vital capacity studies showed the following:

November 4, 1942: 3,200 c.c.

November 11, 1942: 3,200 c.c.

During the following six months he complained only of occasional mild wheezing which was readily relieved by medication. In all he received a total of 18,000 c.c. of oxygen in two periods, 15 and 10 hours, with an increase in vital capacity of 1,000 c.c., or 45 per cent over the pretreatment level, with a marked clinical improvement. After the oxygen therapy he had but one severe attack of asthma in six months, in addition to several mild attacks and an occasional spell of wheezing.

*Case 5.* K. K., age 55, a presser by occupation, was admitted to the allergy clinic on August 13, 1942 with a 25 year history of recurring perennial attacks of choking, wheezing, coughing and labored breathing, usually associated with, or following, upper respiratory infections. In the few years prior to his admission, the symptoms were continuous and severe, with no seasonal or occupational exacerbation. An uncle had asthma.

Examination revealed a small, poorly nourished and developed individual, markedly dyspneic, with a marked retraction of the clavicular fossae and intercostal spaces. Auscultation revealed many sibilant and sonorous râles in both lungs. The heart sounds were distant; there were no murmurs. The blood pressure was 110 mm. Hg systolic and 70 mm. diastolic. An electrocardiogram was suggestive of moderate myocardial damage.

Allergy tests were negative, except for a moderate reaction to dust extract. The nasal examination revealed an allergic type of mucous membrane. On transillumination, all sinuses illuminated clearly except the left maxillary antrum which was practically opaque. Roentgenographic examination showed a clouding of the left maxillary antrum and the presence of an osteolytic destruction of the lateral wall of the left maxillary antrum suggestive of a neoplasm. Roentgenographic examination of the lungs revealed fibrobronchiectasis and old tuberculosis. In addition, there was reported a dense shadow along the outer aspects of the right thorax, opposite the eighth and ninth ribs, encroaching upon the soft tissues, probably of a neoplastic nature. Similar findings, unchanged, were reported upon roentgenographic examination on May 5, 1944, almost two years later. The blood count showed hemoglobin 93 per cent, red blood cells 4,530,000, white blood cells 6,800, with 64 per cent neutrophils and no eosinophils. Urinalysis was negative. Sedimentation rate was 18 mm. in 100 minutes. Blood Wassermann reaction was negative.

The patient was initially admitted to the hospital in August 1942 for study of the tumor of the left antrum, but he refused a biopsy and was discharged in a few days. Severe asthmatic dyspnea continued, however, and he was readmitted to the hospital on October 31, 1942 for intravenous oxygen therapy. The vital capacity determination on the day of admission, during a symptom-free period, was 700 c.c.

Shortly thereafter, he developed an asthmatic attack. Intravenous oxygen was started at 2:00 p.m., the day of admission. At 2:05 p.m. he stated that he was breathing more easily. Objectively, he appeared more comfortable and his respirations were less labored. Intravenous oxygen was continued for five hours. In the third hour of the therapy he developed a severe bronchial spasm which was relieved by one



c.c. of adrenalin. He thereafter passed a comfortable night. The vital capacity determination on the following day, November 1, 1942, was 1,000 c.c., an increase of 300 c.c., or 43 per cent over the pretreatment level.

The same day, November 1, 1942, at 1:30 p.m., he developed a mild asthmatic attack; intravenous oxygen was again administered; the symptoms were relieved; and the oxygen was discontinued after about two hours. At 7:00 p.m. that day, November 1, 1942, moderate wheezing and labored breathing again appeared and intravenous oxygen therapy was resumed. Clinical relief during four hours of therapy was interrupted by a mild attack of asthma and a feeling of precordial distress. Oxygen therapy was discontinued. Because of the precordial distress, further administrations of intravenous oxygen were deemed inadvisable in this patient. The vital capacity determination on the following day, November 2, 1942, was 1,000 c.c. The patient was comfortable until the morning of November 3 when another mild attack was relieved by adrenalin. He was discharged the same day.

During the following three months he had mild daily asthmatic attacks while under treatment at the clinic. After this period his attacks became as frequent and as severe as before the oxygen therapy. The results in this case were unsatisfactory, and any benefit derived might be attributed to bed rest and to the adrenalin injections. However, the oxygen therapy was followed by a period of lessened severity of the asthmatic attacks. The appearance, during the therapy, of precordial distress in this type of patient, in whom a cardiac element was probably of considerable importance, mitigated against further therapy.

In all he received about 4,000 c.c. of oxygen in about 11 hours divided into three periods with a resultant increase in vital capacity of 300 c.c., or 45 per cent above the pretreatment level. This therapy appeared to have had the effect of interrupting the asthmatic attack and of reducing the severity of subsequent attacks for a period of several months.

*Case 6.* H. K., age 58, was admitted to the allergy clinic on January 25, 1940 with a 15 year history of recurring attacks of coughing, choking, wheezing and difficult breathing throughout the year. During the year prior to the admission to the clinic, the attacks occurred nightly, were associated with intense coughing and profuse expectoration, and were becoming progressively worse. There was also a history of dyspnea on exertion and swelling of the extremities. The family history was negative for allergy.

On examination, the patient showed cyanosis of face, lips and fingers. He had a barrel shaped chest. The heart sounds were poor and distant. Wheezing râles were heard throughout the chest, moist râles and diminished breath sounds at the bases. The blood pressure was 172 mm. Hg systolic and 102 mm. diastolic. The liver was enlarged and there was slight pitting edema of the lower extremities. An electrocardiogram showed slurring of all leads, suggesting myocardial fibrosis. Roentgenographic examination of the chest showed moderate emphysema and a diffuse fibrobronchiectasis. The blood count showed hemoglobin 15 gm., and red blood cells 4,400,000. There were no eosinophiles in the blood smear. The sputum was negative for acid fast bacilli. Roentgenographic examination of the sinuses showed a clouding of the right ethmoid sinus and a veiling of both maxillary antra. Nasal examination showed a marked deviation of the septum and polypoid changes in the mid-turbinate. Skin tests failed to yield any definite reactions beyond a slight to moderate reaction to dust extract.

On the basis of this study, a diagnosis was made of chronic bronchial asthma with bronchiectasis (fibrotic) and of hypertensive heart disease with decompensation. Under therapy with digitalis and mercurial diuretics there was moderate improvement. He continued under observation and treatment with both the cardiac and allergy clinics.

In the allergy clinic he was treated with dust extract and with a stock catarrhal vaccine. Local nasal therapy was also employed. Although he improved slightly, his asthmatic attacks continued. On several occasions, antrum washings revealed frank pus. Infected teeth were extracted. In the course of the following year there was little change in his asthmatic picture, while the cardiac picture varied from time to time under the medical regimen outlined above.

He was admitted to the hospital on November 3, 1942 after attending both the cardiac and allergy clinics for a period of two years without any material improvement. The vital capacity determination on admission was 1,000 c.c.

An electrocardiograph tracing on November 3 suggested right ventricular and auricular hypertrophy. Urinalysis showed specific gravities varying from 1.015 to 1.024, an absence of albumin and sugar and the presence of a trace of acetone. Blood urea was 14.6 mg. Blood pressure was 170 mm. Hg systolic and 90 mm. diastolic. A circulation time determination was not made.

He soon developed difficulty in breathing and wheezing, and intravenous oxygen was begun on November 3 at 6:00 p.m. This therapy was continued throughout the night until 10:00 a.m. November 4. During the night of therapy he had no asthma for the first time in two years. The vital capacity determination on November 4, 1942 was 1,600 c.c., an increase of 600 c.c., or 60 per cent over the pretreatment level.

During the evening of November 4, another attack of difficulty in breathing developed. Intravenous oxygen was again started at 7:00 p.m. and continued until 9:00 a.m. on November 5. During the night of therapy he again was comfortable. The vital capacity determination on November 5, 1942 was 1,800 c.c., a further increase of 200 c.c. over the previous vital capacity. Although no further attack developed, he again received oxygen from 7:00 p.m. on November 5, 1942 to 9:00 a.m. on November 6, 1942. During this interval he again was comfortable. The vital capacity determination on November 6, 1942 was 1,800 c.c., unchanged from the previous level. He was discharged from the hospital November 6, 1942.

On the following day he returned to the clinic and reported that he felt well for the first time in two years. One week later he reported that the improvement had continued, and that he had had but one mild attack of asthma which was relieved by an ephedrine capsule within 15 minutes. He stated that before the oxygen therapy he had had three or four attacks nightly for a long period of time. He could now walk three blocks before any dyspnea developed. On February 3, 1943 he reported that his condition was still improved. A vital capacity determination that day was found to be 1,800 c.c., unchanged from the last level, three months previously.

Gradually his wheezing, shortness of breath and asthmatic attacks returned. On July 15, 1943, the opinion of the cardiologist was that his dyspnea was due mainly to a myocardial insufficiency. Owing to the repeated bouts of cardiac decompensation, it was decided to discontinue clinic treatment and to have him admitted to an institution for chronic diseases. In all he received 22,800 c.c. of oxygen in three days in periods of 14, 14 and 10 hours respectively, with an increase in vital capacity of 800 c.c., or 80 per cent above the pretreatment level.

For a period of three months after this treatment, he was free from asthmatic attacks except for one mild spell noted above.

*Case 7.* S. K., a tailor, age 53, was admitted to the allergy clinic on January 29, 1941. Following an attack of influenza with a prolonged convalescence 10 years previously, he developed attacks of labored breathing, wheezing and coughing. At first the attacks were infrequent but gradually they became more frequent and more severe. For the two years preceding his first visit to the clinic, he had constant wheezing and shortness of breath. These symptoms were more intense when he was active, but he was not symptom-free even when at rest. He felt somewhat improved during the summer, and worse during the spring and fall. His maternal uncle had asthma.

On examination his face and hands were cyanotic. Nasal examination revealed a deviated septum, enlarged midturbinates, and some mucopurulent discharge in both nasal chambers. The teeth were in poor condition, the gums inflamed. The heart was not enlarged but the sounds were distant and of poor quality. There were many sibilant and sonorous râles throughout both lungs. There was marked emphysema. No evidence of peripheral edema was noted. The sputum was negative for acid fast bacilli.

Roentgenographic examination showed a diffuse fibrobronchiectasis. The heart was of the aortic type. The electrocardiogram showed moderate myocardial damage and auricular enlargement. On test, he showed marked reaction to dust extract and moderate reactions to feathers, dog hair and silk extracts. He reacted only slightly to the pollen extracts.

From February 25, 1941 to June 1942, he was treated specifically with dust, vaccine and ragweed extracts. Treatment with ragweed extract was included because of the onset of symptoms during the fall and a subsequent exacerbation during that season. In June 1942 the antra were washed and a flaky return was obtained. An autogenous vaccine was prepared from this washing and added to the treatment. In September and October 1942, the attacks became more severe and persistent. Intravenous aminophylline gave only temporary relief.

He was admitted to the hospital on November 6, 1942. The vital capacity determination, during a symptom-free interval, was 1,400 c.c. Intravenous oxygen was started at 8:45 p.m. on November 6, 1942 and continued throughout the night until 9:00 a.m. on November 7, 1942. During the night of therapy he was comfortable.

The vital capacity determination on the following day, November 7, 1942, was 1,600 c.c., an increase of 200 c.c., or 14 per cent above the pretreatment level. Intravenous oxygen was again administered from 9:00 p.m. on November 7, 1942 to 10:30 a.m. on November 8, 1942, and again he spent a comfortable night. He continued symptom-free for the next 24 hours, receiving no oxygen during this period and no adrenalin. The vital capacity determination on November 9, 1942 was 1,900 c.c., a further increase of 300 c.c. over the previous level.

For a period of two weeks he continued improved, had no nocturnal asthma, much less dyspnea on exertion, and generally felt better. After this, his cough returned and, within one month, he again was persistently asthmatic, in spite of further specific therapy, penicillin injections and penicillin aerosol. In all he received 9,600 c.c. of oxygen in two days, given in two periods of 12 hours each, with a resultant increase in vital capacity of 500 c.c., or 36 per cent over pretreatment level. Clinical improvement lasted but two weeks.

*Case 8.* P. C., school girl, age 16, was referred to the allergy clinic on October 17, 1942, after being discharged from the hospital where she had received intravenous oxygen therapy. Her chief complaints were cough, wheezing respiration, difficult breathing and nasal clogging for the past one and one-half years. At the onset, in May 1941, the only complaint was coughing, following a severe upper respiratory infection, but, after February 1942, the cough was associated with attacks of wheezing and difficult breathing. These attacks occurred daily and were relieved by adrenalin injections. There was no seasonal aggravation of symptoms. The family history was negative for allergy.

She was admitted to the hospital on October 9, 1942 for severe and persistent asthma of one month's duration. Examination of the chest revealed typical musical wheezing and whistling râles throughout. The heart was normal; the blood pressure was 128 mm. Hg systolic and 84 mm. diastolic; the blood count showed red blood cells 4,650,000 and a hemoglobin of 90 per cent. The vital capacity determination on admission to the hospital during a free interval was 1,000 c.c.

During the following two days, October 9 and 10, 1942, she coughed at intervals but was fairly comfortable and slept intermittently. At 4:30 a.m. on October 11, 1942 she had a severe asthmatic attack. Intravenous oxygen was started at 5:00 a.m. and was discontinued at 4:30 p.m. that day. During this period she was crying continually, had nausea and headache, but the severity of the asthmatic attack was lessened. At 11:15 p.m. the same day, October 11, 1942, she again had a mild asthmatic attack. Intravenous oxygen was again started but discontinued shortly thereafter as she was very uncoöperative. That night she had some coughing spells but slept at intervals and during the next day, October 12, 1942, she remained fairly comfortable. The vital capacity determination on October 12, 1942 was 1,200 c.c., an increase of 200 c.c., or 20 per cent above the pretreatment level. She was discharged from the hospital on October 12, 1942 stating that she felt considerably relieved, although her wheezing respiration continued as before.

After her discharge from the hospital, she was admitted to the clinic for further treatment on October 17, 1942. There she was tested and showed moderate reactions to dust, feathers and a variety of foods, which were eliminated from her diet. On October 22, 1942, ten days after her oxygen therapy, her attacks were as frequent as before the therapy but less severe and with less cough. In the following week, a mild asthmatic attack occurred which she attributed to the ingestion of cantaloupe and sweet potato, although these foods were negative on skin test. On November 12, 1942, a nasal examination revealed a bilateral, purulent sinusitis, confirmed by roentgen-ray, and involving both ethmoids and both maxillary antra. The roentgenographic examination of the chest revealed a small heart, an accentuation of the root branches, with a general prominence of linear markings. The blood smear showed 8 per cent eosinophiles. The nasal smear showed a predominance of neutrophils with an occasional eosinophilic. The sputum was negative for acid fast bacilli and the urinalysis was negative.

During the following months she was under treatment at the allergy clinic and also in the nose and throat clinic. Frequent bilateral antrum washes revealed purulent returns; her asthmatic attacks continued. A long period of penicillin therapy, both intramuscular and aerosol, yielded but slight improvement at first and later no improvement at all. Radical surgery was resorted to for the infected sinuses with no relief of her symptoms. Subsequent vital capacity studies showed the following:

October 28, 1942: 1,200 c.c.

November 4, 1942: 1,300 c.c.

February 3, 1943: 700 c.c.

In all she received 3,000 c.c. of intravenous oxygen in 12 hours, resulting in an increase in vital capacity of 300 c.c., or 30 per cent, with an immediate slight relief of symptoms during the period of oxygen therapy but with no interruption of her subsequent asthmatic attacks.

This case of bronchial asthma, complicated by a severe paranasal, purulent sinusitis, failed to respond to major sinus surgery on two occasions, to prolonged penicillin therapy, both subcutaneous or aerosol, and to prolonged courses of specific protein therapy. She failed also to respond in any marked degree to the intravenous oxygen therapy. Her attacks have continued severe and recurring throughout the year.

*Case 9.* B. O., age 44, housewife, with a history of recurring attacks of perennial, bronchial asthma for the past 10 years, was transferred from another institution for the purpose of receiving oxygen therapy. Her attacks came on during the day and night and resisted all forms of medication. In addition she was very emotional and neurotic. There was no allergy study in this case prior to her admission to the hospital.

On admission, the vital capacity determination on October 21, 1942 was 1,800 c.c. Intravenous oxygen was started on October 21, 1942 at 7:30 p.m. but was discontinued at 8:00 p.m. because of severity of the dyspnea and the complete lack of coöperation. Adrenalin yielded only slight temporary relief. During the night she was restless, and moaning and crying frequently. She was very emotional and apprehensive.

On the following day, October 22, 1942, she had a mild asthmatic attack. On examination there were many sibilant and sonorous râles throughout both lungs. Intravenous oxygen was started at 5:15 p.m. and the patient felt a general bodily warmth within five minutes with some relief of the bronchospasm. She objected to the needle in the vein, attempting to pull it out repeatedly and the oxygen was discontinued after two hours, at 7:15 p.m. Thereafter she passed a comfortable night, sleeping at intervals, and also passed a comfortable day. At 8:00 p.m. on the following day, October 23, intravenous oxygen was again started but was discontinued after one hour, again because of her emotional state. The vital capacity determination, on October 24, 1942, was 1,900 c.c., an increase of 100 c.c., or 6 per cent over the pretreatment level.

On October 25, 1942 she had several attacks of difficulty in breathing and complained of pains in the chest and cardiac region. Intravenous oxygen was started at 7:45 p.m. and discontinued in five minutes as the patient was very restless, complaining of precordial distress and difficulty in breathing. The vital capacity determination on October 26, 1942 was 1,800 c.c., back to the pretreatment level. She was discharged by ambulance to her own institution on October 26 after refusing further treatment.

Owing to the lack of coöperation and to the emotional state of the patient, oxygen was administered in short intervals with very little effect on either the vital capacity or the frequency of the asthmatic attacks. In all she received 800 c.c. of oxygen with an increase in vital capacity of 100 c.c., or 6 per cent, which was not sustained and may have been within the range of technical error.

## RESULTS AND DISCUSSIONS

Intravenous oxygen therapy was administered in amounts ranging from 3,000 c.c. to 22,000 c.c. in one, two or three stages, in a series of nine cases of severe and persistent bronchial asthma, usually after the onset of an attack. The results in case 9 are not included as the patient was emotional and did not coöperate. The following effects were noted:

1. *On vital capacity:* Following the therapy, the vital capacities in all cases were increased in amounts ranging from 300 c.c., or 30 per cent, to 1,300 c.c., or 87 per cent. This increase was maintained in five cases after one month and in one case after three months. In two cases, subsequent determinations were not made. This increase in vital capacity was lost after three months in three cases and in two cases fell below pretreatment levels in four months and eight months respectively.

2. *On clinical symptoms:* In all cases, there was some degree of immediate relief of clinical symptoms, appearing within five minutes to two hours of the beginning of the therapy. This was evidenced by a very definite lessening of the dyspnea, wheezing respiration and respiratory effort. In four cases a feeling of general bodily warmth developed immediately after the beginning of the therapy. The duration of the clinical improvement varied roughly with the total amounts of oxygen administered. In two

cases, receiving the smallest amounts of oxygen, 3,000 c.c. and 4,000 c.c. respectively, there was a recurrence of all symptoms within 10 days, following only slight immediate improvement. In one case, receiving 9,600 c.c. of oxygen with immediate relief of symptoms, there was a recurrence after one month. In the five remaining cases, receiving from 8,000 c.c. to 22,000 c.c. of oxygen with immediate relief, the clinical improvement was maintained for four to six months. Of this latter group, one was asthma-free for four months and the others had one to two attacks in six months. Several of these attacks were traced to the ingestion of fish and contact with excessive amounts of dust. In all cases but one, the asthmatic attacks returned to pretreatment intensity after six months.

Two cases in this series had exceptionally low initial vital capacities. In one, after 22,000 c.c. of intravenous oxygen, the initial vital capacity of 1,000 c.c. was increased 80 per cent to 1,800 c.c. and was maintained at this level for three months with an absence of asthmatic attacks for four months. In the other, after 9,000 c.c. of intravenous oxygen, the initial vital capacity of 800 c.c. was increased 87 per cent to 1,500 c.c. and was maintained at this level for one month with but one attack of asthma for six months, at the end of which time the vital capacity had returned to a level of 25 per cent above the pretreatment vital capacity.

In the cases presented in this report, the intravenous administration of oxygen to these severe asthmatics yielded prompt relief from the asthmatic paroxysms. Also, there occurred a prompt increase in vital capacities in all cases. These increases persisted after such administrations for periods up to three months and relief of symptoms generally extended beyond the period of increased vital capacity, despite the absence of further such oxygen administration.

Previous investigators have noted that the beneficial results after intravenous oxygen were more permanent than apparently could be explained by the mere relief of cyanosis<sup>2b</sup> and that the improvement in patients seemed to be out of all proportion to the small amounts of oxygen so administered.<sup>2</sup> These facts were noted also in our series of cases. The absence of untoward incidents was believed due to the slow administration and to the low pressure of the flow of oxygen. There is a possibility that the effect of intravenously administered oxygen in asthma was due to an action of the oxygen other than that of relieving an existing anoxemia alone. However, whether or not oxygen so administered acts therapeutically in a manner different from oxygen administered by inhalation can only be conjectured at this time.

More extensive data on various fundamental physiologic effects of intravenous oxygen are needed than the literature presently extant contains. Such investigations must await an apparatus more sensitive and self-regulatory than is yet available.

#### SUMMARY

1. Intravenous oxygen was administered to a series of nine cases of severe bronchial asthma, generally following the onset of an attack.

2. As a result, there was a remission of symptoms immediately in eight cases, lasting from 10 days to six months.

3. There resulted an increase in vital capacities in all cases of from 30 per cent to 87 per cent depending roughly on the amounts of oxygen administered. This increase was lost after three months and fell below pretreatment levels in two cases within eight months.

4. The maintenance of clinical improvement generally extended beyond the period of the maintenance of the increased vital capacity.

5. Very low vital capacities, when sufficiently increased following the intravenous oxygen therapy, yielded beneficial results, even though the resulting vital capacities were still greatly below normal.

6. Whether or not intravenously injected oxygen acts therapeutically in a manner similar to inhaled oxygen can only be conjectured at this time.

We should like to express our thanks to Miss Elsie Kaye, of the department of pathology, for the vital capacity determinations recorded in this study, so painstakingly and patiently performed upon subjects often recalcitrant. We should also like to extend our thanks to Drs. Rothman, Hotkin and Kravchick, of the interne staff, for their coöperation in observing these patients over extended periods during the oxygen administration.

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# PATHOGENESIS OF COCCIDIOIDOMYCOSIS WITH SPECIAL REFERENCE TO PULMONARY ·CAVITATION \*

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It is now accepted that human infections of *Coccidioides immitis* are usually acquired by inhaling the chlamydospores and arthrospores of the fungus. Occasionally the portal of entry may be by abrasions or lacerations.<sup>8</sup> After an incubation period ranging from one to three weeks, symptoms develop in approximately 40 per cent of infected males.<sup>37</sup> However, three-fifths of the infections are completely asymptomatic. The pneumonic or respiratory symptoms which occur in two-fifths are of varying degrees of severity. Among females an increased frequency of erythema nodosum results in a somewhat higher proportion of clinically manifest disease. This erythema nodosum is a complication of the initial infection associated with the hypersensitive state.<sup>10, 35, 38</sup> It occurs in 4 per cent of all coccidioidal infections of white males and one-fifth of their clinically manifest disease.<sup>37</sup> Among adult females it is found in 10 to 25 per cent of their infections and 40 per cent of their clinically manifest disease. Pleural effusion is another occasional complication which occurs relatively soon after the infection is acquired. Even though the fungus is usually recoverable from the pleural fluid, the infection is rarely progressive. A third complication of the primary infection may be pulmonary cavitation and even spontaneous pneumothorax or hydropneumothorax. These complications will be the principal subject of this paper. There continues to be considerable confusion between them and the progressive or disseminating form of infection, coccidioidal granuloma. It is our wish to aid in this clarification and to provide help in distinguishing coccidioidal cavitation from tuberculosis.

Coccidioidal granuloma or disseminated, progressive, or secondary coccidioidal infection, was the only form recognized until Gifford<sup>14</sup> and Dickson<sup>9</sup> reported that *Coccidioides* is the cause of benign "Valley Fever." Its

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From the Commission on Acute Respiratory Diseases, Army Epidemiological Board, Office of the Surgeon General, Department of the Army, and its project for the study of coccidioidomycosis in the Department of Public Health and Preventive Medicine, Stanford University School of Medicine, San Francisco, California. Preliminary studies 1937-1941 were supported by the Rosenberg Foundation.

The data presented are the result of coöperative effort. We cannot express adequately our gratitude even to the extent of listing all who provided histories and replied to our many inquiries. However, in the military hospitals we are especially indebted to Col. Hugh W. Mahon and his colleagues at Fitzsimons General Hospital. Among the civilians the following physicians provided especial aid: W. A. Winn, R. H. Smart, S. L. Goldman, M. A. Gifford and E. Bogen. Appreciation for notable specific collaboration of others is also indicated at the appropriate points of the text.



clinical manifestations are well known: extrapulmonary lesions of lymph nodes, bones, joints, central nervous system, peritoneum, genital tract, skin, mucous membranes of the mouth, indeed, of all organs and of all degrees of severity. The mimicry of extrapulmonary tuberculosis is notorious, as is the 50 per cent case fatality. The military studies<sup>37</sup> have shown that among white adult males approximately 1 in 380 of those infected and 1 in 100 with clinical disease undergo extrapulmonary dissemination. Among Negro adult males the risk of dissemination is at least 10 times as great.<sup>22, 37</sup> Dissemination is much less frequent in females.<sup>2, 15</sup> Army experience<sup>22, 23, 37</sup> also has indicated that dissemination usually occurs soon after the infection is acquired, frequently within a matter of weeks and infrequently after months. It rarely occurs in the second year after the infection, although a few cases are seen. Once dissemination ensues, the risk of continued dissemination is



FIG 1A.



FIG. 1B.

FIG. 1. A and B. Coccidioidal cavity detected in routine coccidioidin survey. Coccidioidin tests negative July 1941 and June 1942 but positive in August 1943. History of malaise, respiratory illness and transient chest pain September 1942. Roentgenogram September 10, 1943, shows cavity in periphery RUL under second rib. *Coccidioides* recovered from sputum. Serology entirely negative. Cavity closed and reopened several times, finally closing permanently November 1944.

great even though remission may occur. Autopsies of those dying of disseminated infections may show lesions of varying periods and lead to the deduction that late disseminations are frequent.<sup>17</sup> However, those observations do not take into account this continued vulnerability of the immuno-



FIG. 2A (i).

logically defective. Among those of us who have handled our infections satisfactorily, the chance of late disseminations is negligible. These statements sound dogmatic and it is regrettable that we do not have time to develop them adequately. We do point out that *none* of our military coccidioid patients, of whom we had records of thousands, has ever been reported to us as having undergone a postwar dissemination. Furthermore, none of the many thousands of service men who were coccidioidin reactors when given their routine test on arrival at their stations was ever known to have undergone dissemination. Disseminations occurred only in those who arrived uninfected, acquired infection and then disseminated. We reiterate

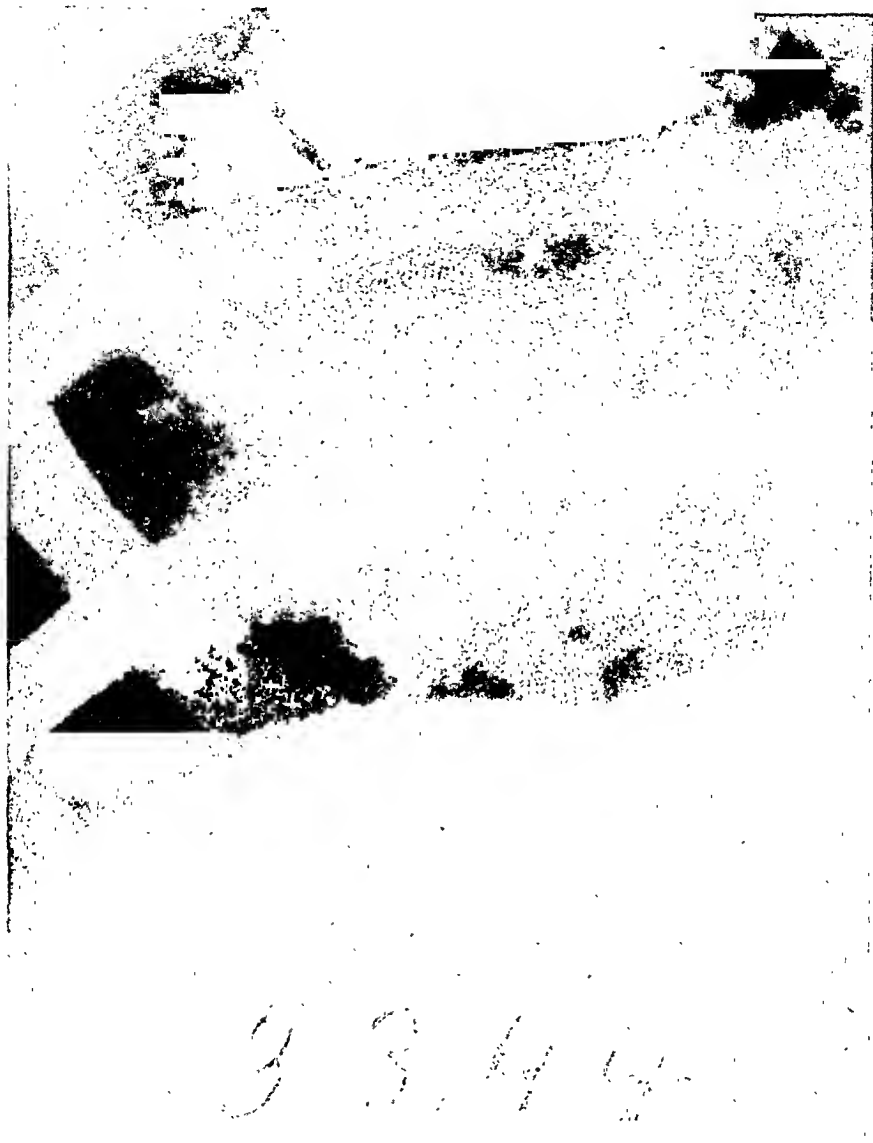


FIG. 2A (ii).

that coccidioidal pulmonary cavitation is not in the category of disseminating or progressive coccidioidal granuloma.

Coccidioidal pulmonary cavitation, first reported in isolated instances by Farness and Mills<sup>11</sup> and Yegian and Kegel<sup>44</sup> and then so excellently described by Winn,<sup>41</sup> is now familiar to us all. The thin wall with little reaction around (figure 1, figure 5A) may cause confusion with lung cysts. Indeed, in recently reviewing our correspondence with Winn, we were interested to see the earnestness with which we discussed whether his cases were cysts with *Coccidioides* implanted or due entirely to the coccidioidal infection. Their very force of numbers drove us to the latter conclusion. The first lobectomy treatment for this condition which is known to us was per-



FIG. 2B (i).

formed by Brunn who described his patient as having lung cysts.<sup>3</sup> The descriptions of Powers and Starks<sup>28</sup> and of Colburn<sup>6</sup> of cavity formation in the acute coccidioidal illness were greatly extended by Sweigert, Turner and Gillespie<sup>39</sup> in their military cases. The most extensive roentgenographic descriptions have been by Jamison<sup>18</sup> and by Jamison and Carter<sup>19</sup> in their presentation of the cavity cases originating in the Western Flying Training Command. There is general agreement that cavities may develop early in the course of the primary illness, often beginning within the pneumonic lesion in a week or two of the onset (figures 2 and 3). On the other hand, the single or multiple pneumonic areas may reduce in size to nodular or irregular



FIG. 2B (ii).

residuals over a period of weeks or months. The patient may be completely over his clinical illness with sedimentation rate normal and serologic tests waning. Then an excavation may develop and a cavity rapidly form. We are not qualified to discuss the mechanism by which these cavities develop and would refer you to papers indicated above.<sup>6, 18, 19, 39, 41</sup> From the immunologic point of view, in only very rare cases is the infection seriously active. We have never seen dissemination occur in a patient with coccidioidal cavitation. Recently Kurz and Loud<sup>21</sup> have reported one, a very unusual case. The patient's pulmonary roentgenogram showed a thin walled solitary cavity which certainly "looked coccidioidal," although no mention was made of whether *Coccidioides* was recovered from the sputum.



FIG. 2C (i).

Within the second year after he had been stationed in a coccidioidal endemic area, trauma resulted in a facial lesion confirmed by biopsy as coccidioidal. Under heavy roentgen therapy it healed completely. Even while the facial lesion was active, the sedimentation rate was only 4 mm. Dr. Reginald Smart<sup>34</sup> informs us of one patient known by him to have had a coccidioidal cavity who died of coccidioidal meningitis. The nearest approach to progressive disease in our series is the case of a Negro dining car worker, a patient of Dr. Smart.<sup>34</sup> He had very extensive cavitation in both lungs with recovery of the fungus from the sputum. The lesions in the lungs were described as progressing. His serum fixed complement in a dilution

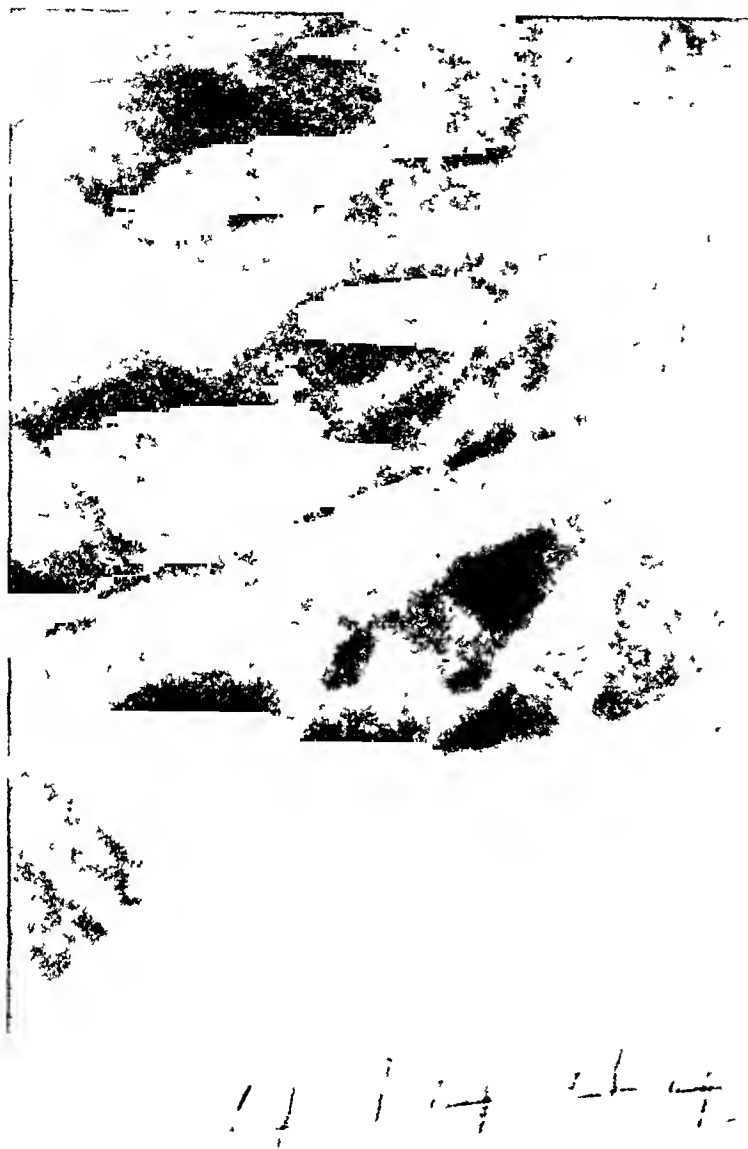


FIG. 2C (ii).

FIG 2 Development of coccidioidal cavity in area of pneumonitis. Recovery of *Coccidioides* from sputum. Positive precipitins and complement fixation. Conversion of coccidioidin.

A. Infiltration in right base three days after onset. Sedimentation rate 25 mm.

B. Beginning cavitation two weeks later. Sedimentation rate 19 mm.

C. Fully developed cavity six weeks after onset. Sedimentation rate 4 mm.

Cavity persisted eight months, closed and reopened several times but after a year remained closed permanently.

of 1:64. His sedimentation rate was very rapid. However, he had no extrapulmonary lesions and when last heard from in 1945, seven years after diagnosis, was still alive. One patient with coccidioidal cavitation was suspected by Dr. Smart as having undergone a bronchogenic spread although his serum complement fixation held at only 1:4. However, he was debili-



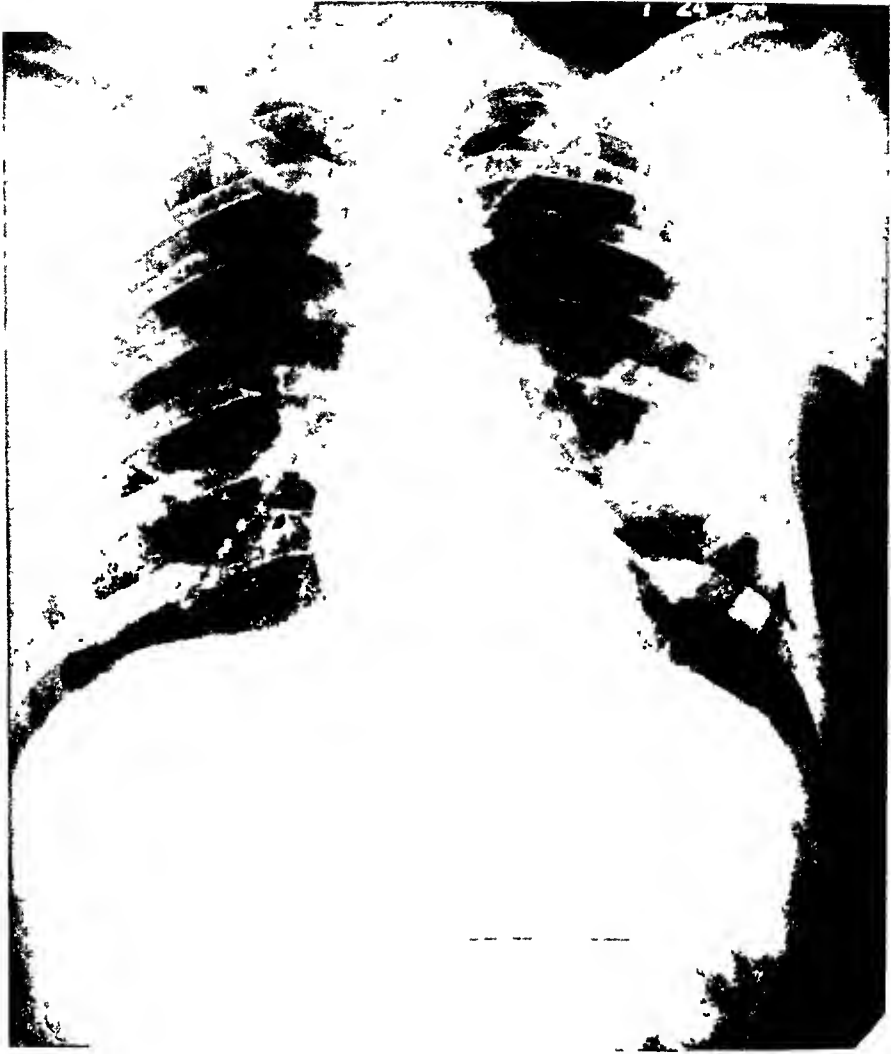


FIG. 3A.

tated by severe and progressive ulcerative colitis. After death in another city, no autopsy was performed. It is apparent that these are unusual cases with complicating features. The consensus of those who have observed both coccidioidal cavitations and disseminations as major complications of the initial coccidioidal infection was aptly phrased by the former Chief of Professional Services at Santa Ana, Dr. George Houck, when he said<sup>17</sup> "While we did not enthuse at the prospect of a patient's prolonged hospitalization, his cavity formation allayed any apprehension of dissemination."

It has been possible to accumulate reasonably accurate data on frequency of dissemination of coccidioidal infection.<sup>37</sup> Estimating the incidence of pulmonary cavitation is much more difficult. The cavity may appear transiently during the acute infection and thus be missed. The cavity may develop months after the acute infection is over, as detection during routine Army roentgenograms showed (figure 4). Thus the association with the

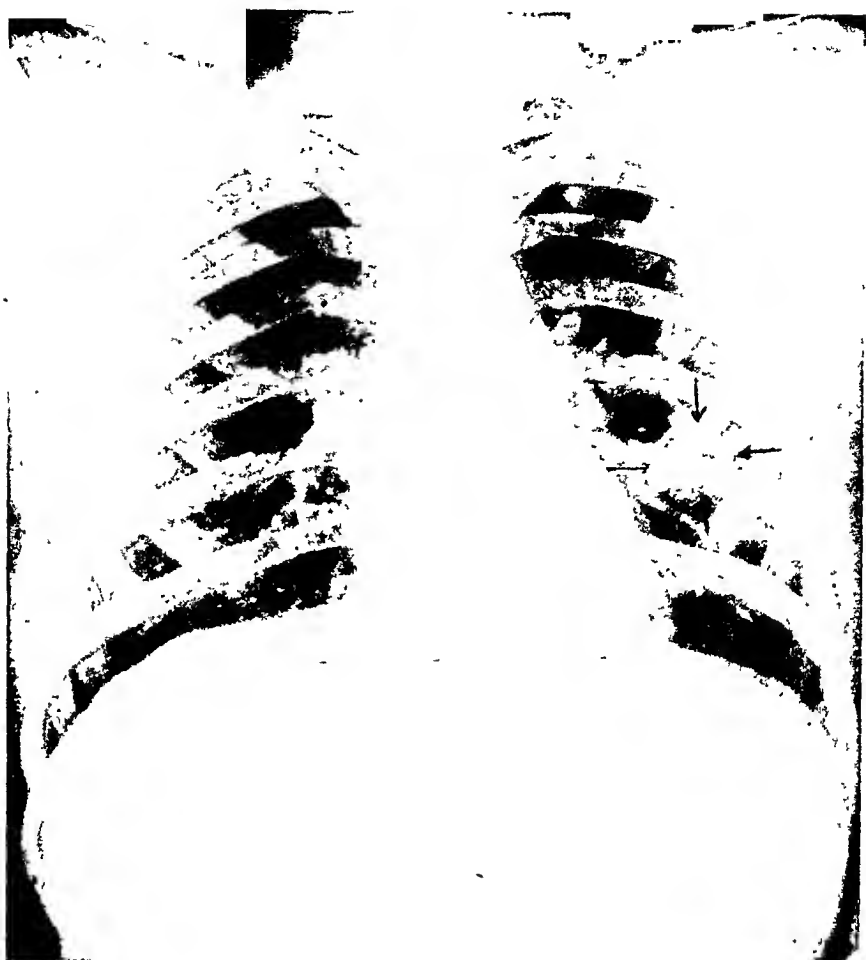


FIG. 3B.

initial infection is readily overlooked. Moreover, cavities may develop after completely inapparent infection. As we shall see, few cavities produce sufficient symptoms to warrant consulting a physician and his ordering a roentgenogram. In the following four studies the frequency of cavitation in clinically manifest primary infection has been calculated. In a study of 77 coccidioidal patients hospitalized at Davis-Monthan Field, Swiegert, Turner and Gillespie<sup>30</sup> reported cavitation in 6 or 8 per cent. Willett and Weiss<sup>40</sup> described cavities in six of 100 coccidioidal patients hospitalized at March Field. Colburn<sup>6</sup> and Goldstein and Louie<sup>16</sup> reported three cavities (4 per cent) in the 75 cases at Camp San Luis Obispo. In our 753 cases of coccidioidal disease hospitalized at Minter, Gardner, Lemoore and Merced Army Air Fields, cavities were detected in 13 or 1.7 per cent.<sup>51</sup> It should be emphasized that these figures apply only to the 25 to 40 per cent of the infections with manifest symptoms. Incidence of cavitation in inapparent infections cannot be estimated. When one recalls the handicaps in the recognition of coccidioidal cavitation, it is very apparent that this complication



FIG. 3C.

is much more frequent than is dissemination. Fortunately, pulmonary cavitation is relatively benign.

Our files contain records of 274 patients with pulmonary cavities which undoubtedly are coccidioidal. One criterion for the coccidioidal etiology was recovery of the fungus (proved culturally and by animal inoculations,<sup>36</sup>

TABLE I

Criteria by Which Coccidioidal Etiology Was Diagnosed on 274 Patients with Pulmonary Cavitation

	No.	%
Cultures positive	109	(40)
Serology positive (cultures negative or not made)	134	(49)
Coccidioidin positive, tuberculin negative (cultures negative or not made; serology negative or equivocal)	31	(11)
	<hr/> 274	<hr/> (100)

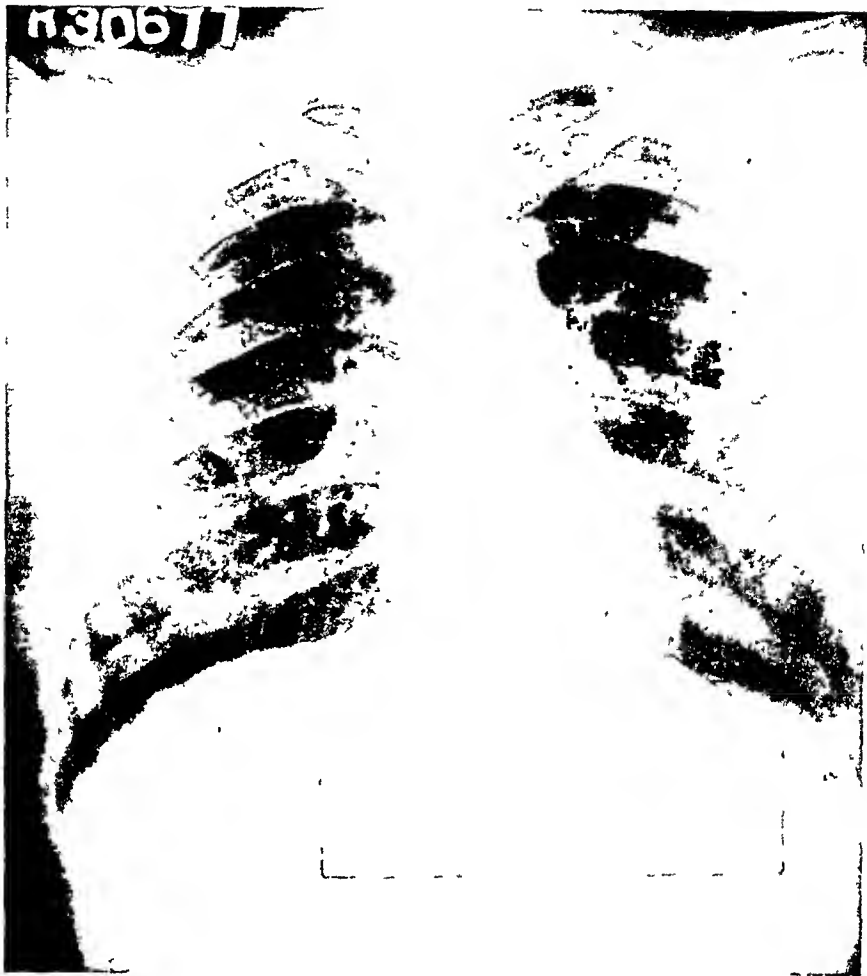


FIG. 3C (i).

not by undependable coverslip examination of sputum) (table 1). A second acceptable criterion was demonstration of positive serology, precipitins during the acute phase or complete fixation of complement in at least the first (1:2) dilution of serum. The third acceptable group had positive coccidioidin and negative tuberculin tests. Even though the cavity looked "typical" and the patient had a positive coccidioidin reaction and partial complement fixation, if his tuberculin test was positive or was never performed, he was not included. We excluded 87 patients whose cavities were reported to be coccidioidal but who could not meet these standards. It must be admitted that we ourselves did not see the roentgenograms of most of these patients and had to depend on the opinion of others. We excluded all in which there was any expression of doubt, such as "emphysematous bleb" or "*possible cavity*." Of the 169 from military and veterans hospitals 128 were from General and Regional Hospitals and 15 from Veterans Hospitals. The Chief of Professional Service at the Santa Ana Army Air

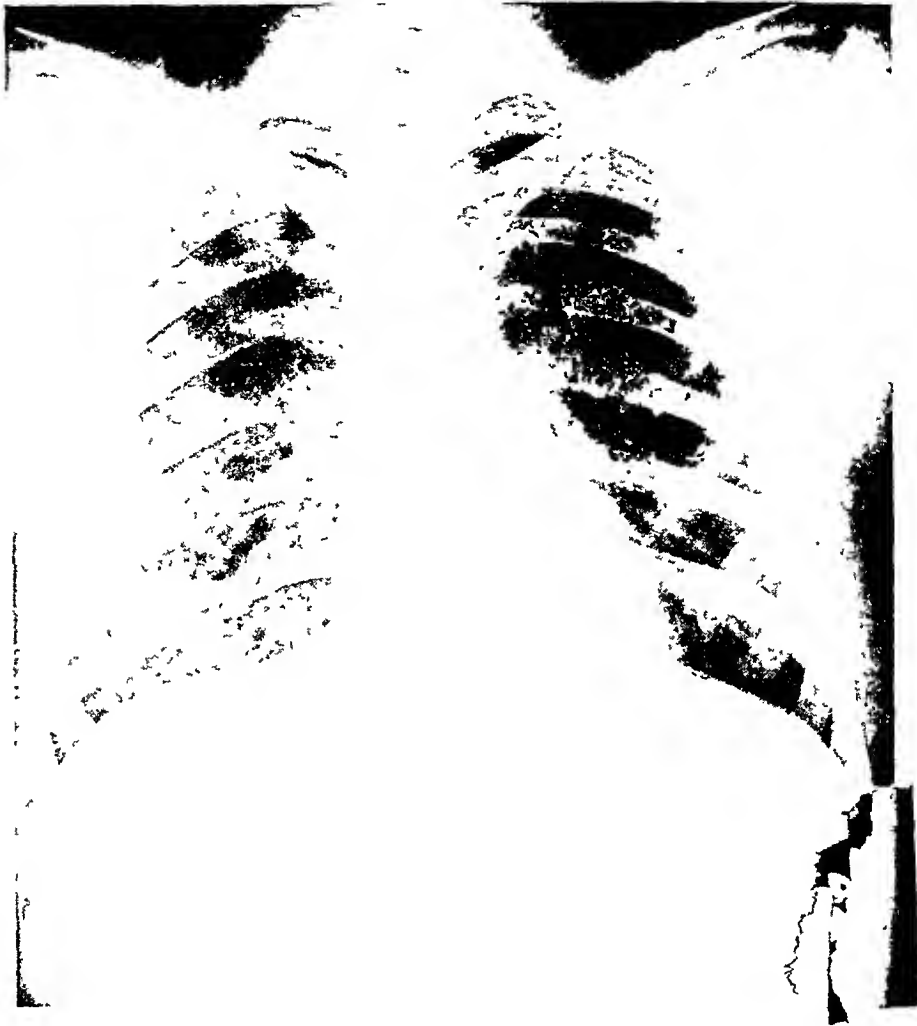


FIG. 3D.

FIG. 3. Development of coccidioidal cavity in residual nummular area and eventual disappearance. No sputum studies made. Complement fixed through 1:4 serum dilution; precipitins present initially. Conversion of coccidioidin skin test.

A. Pneumonic lesion in left lower lung two days after onset. Sedimentation rate 18 mm.

B. Resolution of infiltration to residual nummular lesion but beginning cavity formation 25 days after onset. Sedimentation rate 9 mm.

C. Well-defined cavity  $2\frac{1}{2}$  months after onset. Sedimentation rate "normal." (i) Anterior-posterior view. (ii) Lateral view.

Cavity continued clearly defined for six months, then less sharply outlined.

D. Lung clear one year after onset. Sedimentation rate 4 mm.

Lung still clear two years later and sedimentation rate 4 mm. However, complement still fixed through 1:4 dilution, the same titer as at onset.

Base<sup>17</sup> has declared that in his experience the coccidioidal cavities were never "over-read" but the errors of the stations hospitals of the Western Flying Training Command which "fed" into Santa Ana were in overlooking them. Of the 105 cavities observed in civilians, 92 were diagnosed by recognized phthisiologists. Some of these cavities may have been "phantom," but when we note that 89 per cent of the etiological diagnoses were based on cultures

or serology, the coccidioidal mischief is clear-cut. An occasional bronchiectatic focus might account for a positive sputum, but this complication is much rarer than cavitation.

A possible pitfall in diagnosing the etiology of cavitation may be infection with both *M. tuberculosis* and *C. immitis*. Proof of one infection may terminate studies which would have revealed the other, too. Double infections have been reported in three patients by Cherry and Bartlett<sup>4</sup> and in a patient with spontaneous hydropneumothorax by Rifkin, Feldman, Hawes and Gordon.<sup>29</sup> Included in our group are seven more double infections. Both organisms were recovered from five. In the other two, *M. tuberculosis* was recovered and the rôle of *Coccidioides* was indicated by fixation of serum to a diagnostic titer. Whether persistent search for *Coccidioides* would have revealed the fungus also, we cannot say. In only one of these cases, a Negro reported by Dr. W. L. Nalls<sup>26</sup> at the Oteen, N. C., Veterans Hospital, did the tuberculous infection appear to be progressive. In no instance did the coccidioidal infection progress. Certainly coccidioidal infections rarely "activate" a quiescent tuberculous infection. In only one of 753 patients hospitalized with coccidioidomycosis<sup>31</sup> did we discover active clinical tuberculosis. On one occasion we visited a military hospital located in such a highly endemic coccidioidal area that 50 per cent of the susceptibles stationed in the region acquired coccidioidal infections within six months. Because of the dry warm climate, tuberculous patients were being brought in for treatment. Although their only exposures were in the hospital wards, we discovered that 11 had acquired coccidioidal infections. Ubiquitous desert dust supplied the infecting chlamydo-spores. In none of the 11 was the coccidioidal infection especially severe, though one did develop a coccidioidal effusion on the side opposite that in which had appeared the tuberculous effusion which necessitated his hospitalization. The clinicians caring for the patients stated that the coccidioidal infections had not hampered the healing of the tuberculosis. However, we may note that coccidioidal pulmonary cavitation does not preclude active tuberculosis or vice versa.

Our data do not permit an adequate analysis of the symptoms associated with pulmonary cavitation. However, in 224 of the 274 we are able to present the reason why the roentgenogram was taken which revealed the lesion. In table 2 we observe that in nearly three-fifths of the military group these were routine films. In 25 the routine films were made on separation from the service; in four of the 12 "incidental illnesses" the pictures were taken in the course of the chest surveys of the wounded. These findings bespeak the characteristically "silent" character of these lesions. One notes that in the civilian group only one-quarter were detected as "silent" lesions. Of course this is not because of the more severe nature of lesions in civilians but because roentgenograms are much less frequently taken. This point is further borne out by the fact that the proportion of the coccidioidal

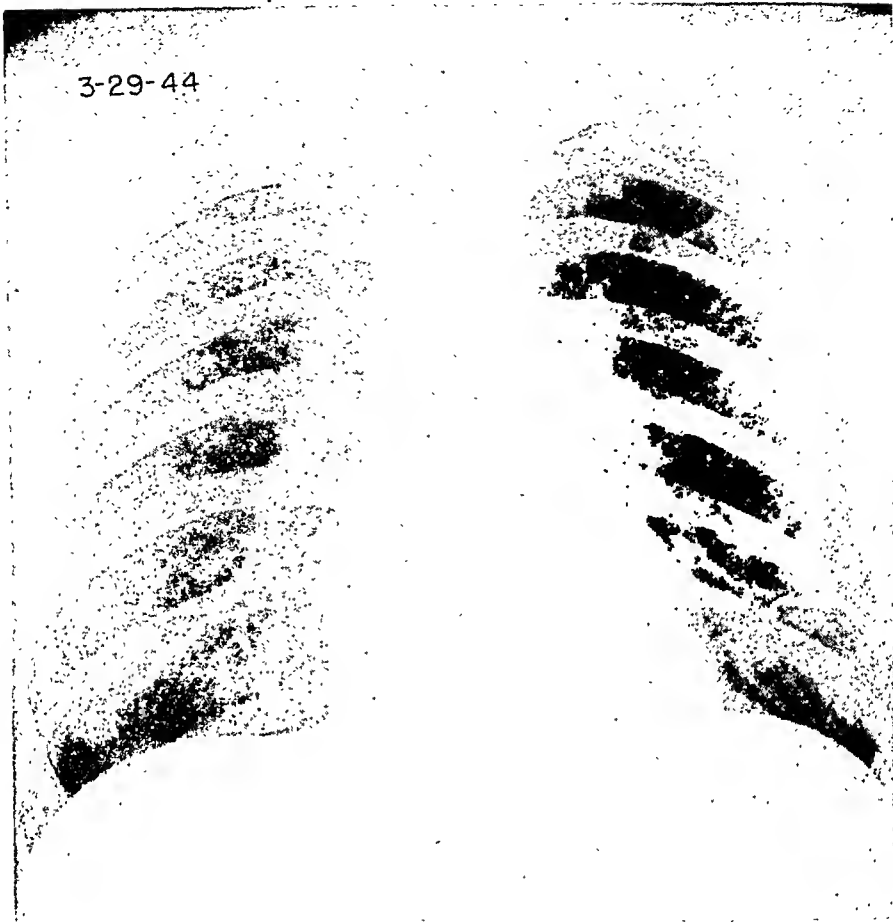


FIG. 4A.

cavities detected in the course of clinical illness was twice as high in the military as in the civilian group. One notes that the outstanding sign or symptom produced by the cavitation was hemoptysis. Nearly three-fifths of the civilian group were detected because of that danger sign. It was

TABLE II  
Reasons for Taking Roentgenograms Which Resulted in 224 Diagnoses of Coccidioidal Pulmonary Cavitations

	Military No. (%)	Civilian No. (%)
Routine (no illness)	73 (48)	14 (20)
For another illness	12 (8)	3 (4)
Coccidioidin survey	3 (2)	0
Total incidental discoveries	88 (58)	17 (24)
Hemoptysis	24 (15)	40 (57)
Chest pain	9 (6)	2 (3)
Cough, malaise, fever or sputum	6 (4)	6 (8)
Course of acute coccidioidomycosis	26 (17)	6 (8)
Total with specific symptoms	65 (42)	54 (76)
ALL	153 (100)	71 (100)



FIG. 4B.

FIG. 4. Development of multilocular cavity from infiltration accompanying asymptomatic infection. *Coccidioides* constantly recoverable from sputum. Complement fixation through 1:8 serum dilution. Positive coccidioidin test. Sedimentation rate consistently normal.

A. Routine survey roentgenogram to qualify for overseas service. Extensive infiltration right apex with negative tuberculin. No preceding symptoms. Despite prolonged bed rest cavities gradually developed.

B. Multilocular cavities present in site of old infiltration 11 months later. Sedimentation rate still normal.

Subsequently developed considerable sputum and frequent hemoptysis. Two years after diagnosis complement fixed 1:32. Lobectomy 1948.

rarely sufficient to menace health, but was often so frequent and alarming as to make the victim unemployable. Chest pain, cough, malaise, fever or excessive sputum accounted for only one-tenth of the military and civilian discoveries. Thus the benign clinical nature of most coccidioidal pulmonary cavities is notable. They are in marked contrast to the fever, malaise, asthenia and severity of the illness observed in disseminated coccidioidal infection (coccidioidal granuloma).

In 269 we could note the number of cavities. While a solitary cavity is "characteristic," multiple coccidioidal cavities do occur. As table 3 indi-



cates, nine-tenths were single. Four per cent were multilocular (figure 4). As noted in table 4, there seemed no outstanding predilection for right or left side (45 per cent left; 55 per cent right). With respect to the location in the various lobes, we were reluctant to accept a statement respecting the particular lobe involved. Very frequently a lesion will appear to be in the upper lobe when it actually involves the upper portion of the right middle or

TABLE III  
Number of Pulmonary Cavities Stated to Be Present

Classification	No.	%
Single	241	(90)
Multiple (two, 9; three, 1; four, 1; "several," 6)	17	(6)
Multilocular	11	(4)
	<hr/> 269	<hr/> (100)

TABLE IV  
Location of the Coccidioidal Pulmonary Cavities

Left upper chest (16 "apical")	71
Left lower chest	19
Left chest (location not specified)	7
	<hr/>
Total left chest	97
Right upper chest (12 "apical")	77
Right lower chest	45
Right chest (location not specified)	6
	<hr/>
Total right chest	128
Total, left and right <i>upper</i> chest	148 (70%)
Total, left and right <i>lower</i> chest	64 (30%)

of a lower lobe. By tabulations on the basis of "upper" or "lower" chest we observed that 70 per cent were "upper" and 30 per cent "lower." One-eighth were actually reported as "apical," posing emphatically the question of differentiation from tuberculosis.

The first step in the diagnosis of coccidioidal infection is the application of a coccidioidin skin test. This material is the filtrate of asparagine synthetic broth medium, the preparation and use of which have recently been described quite fully.<sup>38</sup> As we have pointed out, a strong reaction does not activate or disseminate a coccidioidal infection, nor does it complicate diagnosis by stimulating the diagnostic precipitins or complement fixing antibodies. When concentrations greater than 1:100 are used, non-specific cross reactions may be confusing, especially in reactors to histoplasmin. However, it must be admitted that in our group of patients with cavities, excluding those diagnosed on the basis of positive coccidioidin and negative tuberculin, 10 per cent were reported to be negative to 1:100 coccidioidin (table 5). Of those diagnosed by culture, one-sixth did not react to 1:100 coccidioidin. Most of those who did not react to 1:100 dilution were posi-

tive to 1:10 coccidioidin. Sometimes they would be completely negative to 1:100 coccidioidin but show a reaction 7 centimeters in diameter with 1:10 material. Three or 3 per cent of the culture positive diagnostic group were stated to be negative to 1:10 coccidioidin. Two of these patients were tested with autogenous coccidioidins made from their homologous strains. One patient did not react to his own, either, while the other is said to have reacted to his autogenous coccidioidin in 1:100 dilution. One's immediate inclination is to hypothecate an antigenic difference in the strains. Such a

TABLE V  
Coccidioidin Sensitivity of Patients with Coccidioidal Pulmonary Cavitation\*

Diagnostic Group*	Reaction to Coccidioidin								Total	
	Pos. 1:100 (or more dilute)		Neg. 1:100 Pos. 1:10		Neg. 1:100 (not test 1:10)		Neg. 1:10			
	No.	%	No.	%	No.	%	No.	%	No.	%
Culture Pos.	85	(84)	8	(8)	5	(5)	3	(3)	101	(100)
Serum Pos.	127	(95)	5	(4)	2	(1)	0	(0)	134	(100)
Combined	212	(90)	13	(6)	7	(3)	3	(1)	235	(100)

\* Group diagnosed on basis positive coccidioidin and negative tuberculin omitted.

situation has never been observed by us in rather extensive studies we have carried out.<sup>1, 38</sup> We have tried to guard against such a theoretical eventuality by including multiple strains as inoculants for our coccidioidins. Evidence that the "strains" did "cover" the three non-reactors is seen in the fact that the patient who reacted to his autogenous coccidioidin but not to our "stock" nevertheless had clear cut serum complement fixation (1:2 + + + +, 1:4 + + +, 1:8 + +) against antigens which had been prepared from the same strains as were used in preparing the skin testing coccidioidin. The patient who reacted neither to his own nor to our stock coccidioidin had complete fixation of complement in 1:4 serum dilution. The other patient listed as negative to stock 1:10 showed + + + fixation in 1:2 serum dilution. It is clear that the diagnostic humoral antibodies were "covered" antigenically. Indeed, when we tried the autogenous coccidioidin against the homologous serum, it failed to fix complement as effectively as did our stock complement fixing antigen. The failures of the autogenous antigen in complement fixation reflect the fact that satisfactory complement fixing antigen is not easy to prepare. We suspect that the difficulty with the coccidioidin may be associated with various fractions of the coccidioidin. Especially in patients with coccidioidal cavities, the reaction to coccidioidin may be a faint blush, though with considerable induration which is maximal in 24 hours and gone in 48 hours. We had two other patients with coccidioidal cavities reported as failing to react to 1:10 coccidioidin. When the patients were trans-

ferred to Santa Ana Army Air Base, Captain Charles D. Marple<sup>25</sup> tested them personally and found that the men reacted vigorously at 24 hours, though with this faint, easily missed erythema and induration. Readings of the coccidioidin test should be made at 24 and 48 hours. Induration over 5 mm. should be read as positive at either period. Whether these conditions were met in the three patients recorded as negative to our stock coccidioidin in 1:10 dilution is not known. We have noted marked variation in interpretations of the coccidioidin results. In the excellent detailed medical records accompanying specimens sent us from Fitzsimons General Hospital, sometimes one would note the coccidioidin recorded as positive in several army hospitals and negative in others. Properly used and interpreted, the coccidioidin test is the most important and useful "screen." However, like every biological test, it is not perfect.

Of proved aid in diagnosis of coccidioidal infection are precipitin and complement fixation tests.<sup>36</sup> Both tests are generally negative in mild, "inapparent" coccidioidal infections. The precipitins appear before complement fixing antibodies but if the latter do appear, they generally persist longer. With a few exceptions, precipitins disappear within a month or two after the infection has been acquired. By the time most cavities have been discovered, precipitins have vanished. In the group of 134 patients with coccidioidal pulmonary cavitation diagnosed by serological evidence, eight patients showed only positive precipitins. Their cavities developed during the acute coccidioidal illness or in a pneumonic area which appeared during the illness. Thus precipitins may be of use in clinching the etiology of a cavity which appears as a complication of the acute coccidioidal respiratory illness. Once the initial illness is over, the complement fixation test of the serum provides a very important means of aiding in the diagnosis.

In evaluating the efficacy of serological tests in establishing coccidioidal etiology of pulmonary cavitation, we must be restricted to the group in which the fungus was recovered. It should be noted that this restriction selects adversely against the diagnostic significance of the serological tests, for in a considerable number of instances the search for *Coccidioides* was

TABLE VI  
Coccidioidal Complement Fixation in 107 Patients with Pulmonary Cavitation;  
*Coccidioides immitis* Cultured from Sputum

Complement Fixation	Serum Dilution	No.	%
Negative (or +)	1:2	28	(26)
Equivocal (6+++; 7++++)	1:2	13	(12)
Complete (++++)	1:2	31	(29)
Complete (++++)	1:4	20	(19)
Complete (++++)	1:8	8	(7)
Complete (++++)	1:16	5	(5)
Complete (++++)	1:32	1	(1)
Complete (++++)	1:64	1	(1)
		107	(100)

made and continued until the fungus was demonstrated because the serological tests could not clinch the diagnosis. As table 6 shows, the sera of approximately three-fifths of the culture positive group fixed complement to a diagnostic titer. One-quarter were entirely negative. These facts emphasize that in a very considerable number of instances the etiology of a suspected coccidioidal cavity can be established only by recovery of the fungus.

The frequency of negative or equivocal complement fixation and the relatively low titer of the complement fixation which does occur are in striking contrast to the high titer of complement fixation observed in disseminated coccidioidal infection (coccidioidal granuloma). In table 7 is

TABLE VII  
Coccidioidal Complement Fixation Titer in 192 Coccidioidal Pulmonary Cavity  
Patients with Positive Serology

Highest Serum Dilution Showing Complete Fixation	No.	%
1:2	101	(53)
1:4	58	(30)
1:8	21	(11)
1:16	10	(5)
1:32	1	( $\frac{1}{2}$ )
1:64	1	( $\frac{1}{2}$ )
	<hr/> 192	<hr/> (100)

presented the range in titers of 192 patients with coccidioidal cavitation whose serum fixed complement to a diagnostic titer. Half had complete fixation only in 1:2 serum dilution and 94 per cent went only through 1:8 serum dilution. We have not analyzed all of our complement fixation results in coccidioidal granuloma patients, but seven-eighths certainly fix complement to a higher serum dilution than 1:16. Only two in the cavity group ran up to this usual "range of dissemination."

Observation of serology as cavities developed also elicited evidence against cavity formation implying actual progression of the infective process. We have alluded to the fact that in eight instances, only precipitins were demonstrable before or during the process of cavitation. Among those whose serum fixed complement, three showed no significant change and five showed actual regression by at least one serial dilution as the cavities formed. The presence or absence of the mechanical defect appeared to have no significant influence on the titer of the complement fixation. In three instances we observed the same titer prior to and during cavitation and also after the cavity had closed.

The sedimentation rates seen in table 8 provide further evidence that the infection is usually not active in patients with coccidioidal pulmonary cavities. In nearly three-quarters the rates were normal. Even as cavities were developing, the sedimentation rate would usually return to normal. A few rates continued to be elevated but this is also observed in convalescence

TABLE VIII

Frequency of Accelerated Sedimentation Rates in 149 Patients with Coccidioidal Pulmonary Cavitation by Diagnostic Group

Diagnostic Group	Sedimentation Rate				Total	
	Increased		Normal			
	No.	(%)	No.	(%)	No.	(%)
Culture positive	17	(30)	39	(70)	56	(100)
Serum positive	20	(28)	51	(72)	71	(100)
Coccidioidin pos. } Tuberculin neg. }	4	(18)	18	(82)	22	(100)
ALL	41	(28)	108	(72)	149	(100)

without cavitation. In contrast, patients with active coccidioidal infections, during either the initial respiratory illness or progressive coccidioidal granuloma nearly always have very accelerated sedimentation rates. While normal sedimentation rates may sometimes be seen in tuberculous cavitation, persistently normal rates are more frequently observed in coccidioidal cavitation.

An understanding of the pathogenesis of these cavities is necessary in deciding on treatment. That these cavities are very likely to remain open is well known. Jamison<sup>18</sup> noted that 19 of his 35 coccidioidal cavities were still open after an average follow-up period of 7½ months. In our series cavities were known to have been present and still open after at least six months of observation in 82 cases. Seventy-two were open over one year, 37 over two years, 25 over three years, 14 over four years and 3 over ten years. From the histories of hemoptysis it is certain that cavities had persisted much longer, but these figures are for actual years of observation of the cavities. In our series only 31, less than half as many of the cavities were reported to have closed, 12 within six months' time and 22 within one year. Three were reported to have closed in the second year of observation, a like number in the third year and one each in the fourth and fifth year. Probably unbeknownst to us many others closed, for usually our facilities were used only for diagnosis and our attempts at follow up of patients from the military-veteran group have not been very successful.

In most instances coccidioidal cavities do not menace the health of the patient. Often he can lead an entirely normal life even if it stays open. We once feared late disseminations and suspected that these patients might develop meningitis or other disasters. However, our experience with lobectomy<sup>27</sup> convinced us that endogenous as well as exogenous reinfection is extremely unlikely. As we noted, this patient's operation was in 1940 prior to the era of chemotherapy. Postoperative empyema resulted in a bronchopleural fistula and extensive sinus formation. Despite the fact that along with pyogenic bacteria the fungus drained from her chest for nearly

four years, she had no metastatic lesions nor extension either to the opposite lung or to the lower lobe of the affected side. Her sinus closed after thoracoplasty and she has been entirely well for four years. The excellent results now being reported in lung surgery for coccidioidal cavitation are further proof that spread from the lesion would be very exceptional, since postoperative extension or spread has never been reported. Thus, unless there is definite indication such as repeated hemoptysis or the troublesome coughing or chest pain which occasionally ensues, the patient may well be left alone to live with his cavity. Unfortunately, a mistaken analogy with tuberculosis is apt to drive us into taking drastic steps which the health of the patient does not warrant.

The possibility of contagion is another reason why vigorous efforts to close a cavity might be undertaken. This point has been discussed previously.<sup>27, 41</sup> There has been general agreement that *Coccidioides* in the sputum does not pose a public health problem. Epidemiological evidence has emphasized the infectiveness of the tiny chlamydo-spores and arthrospores of dry mycelia. Large numbers of known laboratory infections, infections recognized as having been acquired merely by driving or riding on trains through endemic areas, infections acquired merely by contact with dusty products or clothing—these are eloquent proof of this high infectivity. By contrast, the spherules (sporangia) seen in animal tissues seem poorly adapted to contagion. Rosenthal and Routien<sup>32, 33</sup> recently raised the specter of contagion. In their experiments to demonstrate contagion they exposed tracheas of guinea pigs and then injected spherule-containing pus or sputum into the tracheas and down into the lungs. Naturally enough, lesions developed in the lungs, but a clinical analogy seems remote. There is not space in this paper to discuss adequately the subject of contagion.

It should be stated, however, that in two patients at Fitzsimons General Hospital<sup>24</sup> and one at Baxter General Hospital,<sup>43</sup> coccidioidal cavities removed surgically were observed to contain *Coccidioides* in mycelial form. Thus chlamydo-spores from dried sputum might float to others just as limited development of mycelia could occur if sporangia-containing pus or sputum was deposited in a moist dark corner. However, all evidence indicates that ordinary hygienic precautions suffice to prevent "contagion." Contrasting with recognition of *laboratory* infections in seven Army hospitals with which we collaborated, no "contact" infection in a ward attendant, nurse or physician has ever been made known to us. Also, though these numbers are small, we have accumulated some "negative" evidence. Our patient previously mentioned convalesced from her lobectomy and spent most of her summers with her parents-in-law. She lived in the San Joaquin Valley. They resided on the coast near San Francisco. We calculated that she lived in their house for a total of five *proved* sputum-positive years and one and one-half years when she also had dressings soaked with pus proved to contain *Coccidioides*. However, both of her parents-in-law failed to react to 1:10 coccidioidin. The veteran whose multilocular cavity is seen in

figure 4, had abundant *Coccidioides* in his sputum up to the time that Dr. Alfred Goldman removed his affected right upper and middle lobes. At the time of the operation his son was six months old. Dr. Robert S. Cleland obligingly coccidioidin tested the baby two months after the surgery and the baby failed to react to 1:100 coccidioidin.<sup>5</sup> A First Sergeant in Letterman General Hospital with a pulmonary cavity had sputum and gastric contents consistently positive for *Coccidioides*. Captain T. G. Kabza<sup>20</sup> kindly tested the wife and 18 months old son with 1:100 coccidioidin without eliciting any response. We have tested the wife of another veteran with a persisting cavity from which *Coccidioides* was recovered at one time. She did not react even to 1:10 coccidioidin, but at the time of her test *Coccidioides* could not be recovered from his sputum, the cavity appearing to be blocked. None of these patients had attempted "isolation" measures, though they were intelligent and presumably had observed conventions of ordinary decency. While five, possibly six, proved exposures of susceptibles is small and criticism may be made that even tuberculosis does not infect at once, it seems fair to conclude that contagion from coccidioidal cavities certainly is not rampant. No one seriously proposes barring travel through coccidioidal endemic areas though resultant infections are proved. Thus the case for preventing exotic coccidioidomycosis by such a "travel quarantine" would seem more plausible than by imposing isolation procedures on patients. A corollary is that closure of a coccidioidal cavity does not seem imperative on the grounds of public health which apply to "sputum positive" tuberculous cavities.

We formerly shared with Winn<sup>42</sup> some enthusiasm for pneumothorax treatment. In six of our group closure of a cavity was reported following institution of pneumothorax. Willett and Weiss<sup>40</sup> reported the closure of one cavity after a pleural effusion and we noted two others. In one additional patient effusion occurred as a complication of pneumothorax treatment and the cavity remained closed after the fluid absorbed. While pneumothorax treatment apparently has aided some patients, in 10 of our group the treatment is known to have failed. Either the cavity was not closed or if it did close it reopened. This reappearance of a once-closed cavity is most discouraging. An explanation of why some cavities do not remain closed may be the several reports we have received of epithelialization of cavity linings. A contraindication to pneumothorax is a subpleural cavity. Collapsing the lung brings the very real danger of bronchopleural fistula and spontaneous hydropneumothorax.

Treatment by phrenic crush as advocated by Denenholz and Cheney<sup>7</sup> is credited with closing at least four of the cavities of this group. Incidentally, the closure of the three and four year old cavities mentioned previously occurred after phrenic interruption. With his very considerable experience in this field, Willett is optimistic about this treatment. Obviously, it is not a sure cure. In our group a half-dozen were not benefited by its use. However, its benign nature recommends it for appropriate cases.

It would appear that if cavitation develops during the initial infection, strict bed rest should be continued even after temperature and sedimentation rate seem normal. However, with old cavities it must be admitted that bed rest alone has rarely proved useful, as Jamison's experience also indicates. Denenholz and Cheney<sup>7</sup> combined it with shot bag immobilization, though this, too, has limited use. Our own faith in the value of rest was badly shaken by an experience at Minter Field. Convalescing from a coccidioidal pneumonitis he developed in May, one of the enlisted men in the Medical Detachment developed a cavity in the area of consolidation. He was kept in bed several months and then cautiously allowed up. His cavity gradually closing, he was discharged from the hospital, but was excused from physical training and restricted in his duties. We congratulated ourselves on how splendidly we were managing him until we discovered his cavity closure had been completed while he was the star end of the Minter Field football team.

When coccidioidal cavities evoke symptoms but fail to close on a trial of rest or phrenic crush, lung surgery may be undertaken without misgiving. Our former emphatic stand against such radical treatment resulted from the complications in our patient following lobectomy.<sup>27</sup> However, her difficulties would not have arisen had antibiotics been available in 1940. Lobectomies and resections have succeeded in a score of patients with coccidioidal cavities. Recently Rogers<sup>30</sup> merely shelled out a thin-walled coccidioidal cavity and approximated the lung tissue. Controlling bacteria with antibiotics results in uncomplicated healing. An operation does not stir up infection even to the extent of increasing the titer of complement fixation. In four patients postoperative serological titers continued negative. One had a postoperative pneumonia, but the absence of complement fixation indicated that *Coccidioides* was not responsible. Of four instances in which serum fixed complement prior to lobectomy, the titers fell one serial dilution immediately after operation. However, they continued at that reduced level. It would appear that part but by no means all of the infected tissue had been removed. Roger's patient from whom the cavity merely had been excised showed no change in low but conclusive (++++) in 1:2) complement fixation. Thus surgery can be performed for coccidioidal cavitation without dissemination and even without local spread as long as bacterial infection is kept under control. Apparently *Coccidioides* poses no special risk. Except in the immunologically defective "disseminators," coccidioidal immunity is surprisingly solid. Since we consider any thoracotomy is serious, we do not advise lung surgery unless a cavity really causes disability. Furthermore, a word of caution is advisable. While immediate results of this lung surgery have been excellent, follow up to eliminate possibility of unforeseen complications is imperative.

However, even though "silent," peripheral (subpleural) persistent coccidioidal cavities may well warrant "prophylactic" lung surgery. Regardless of how one regards pneumothorax treatment of coccidioidal cavities in



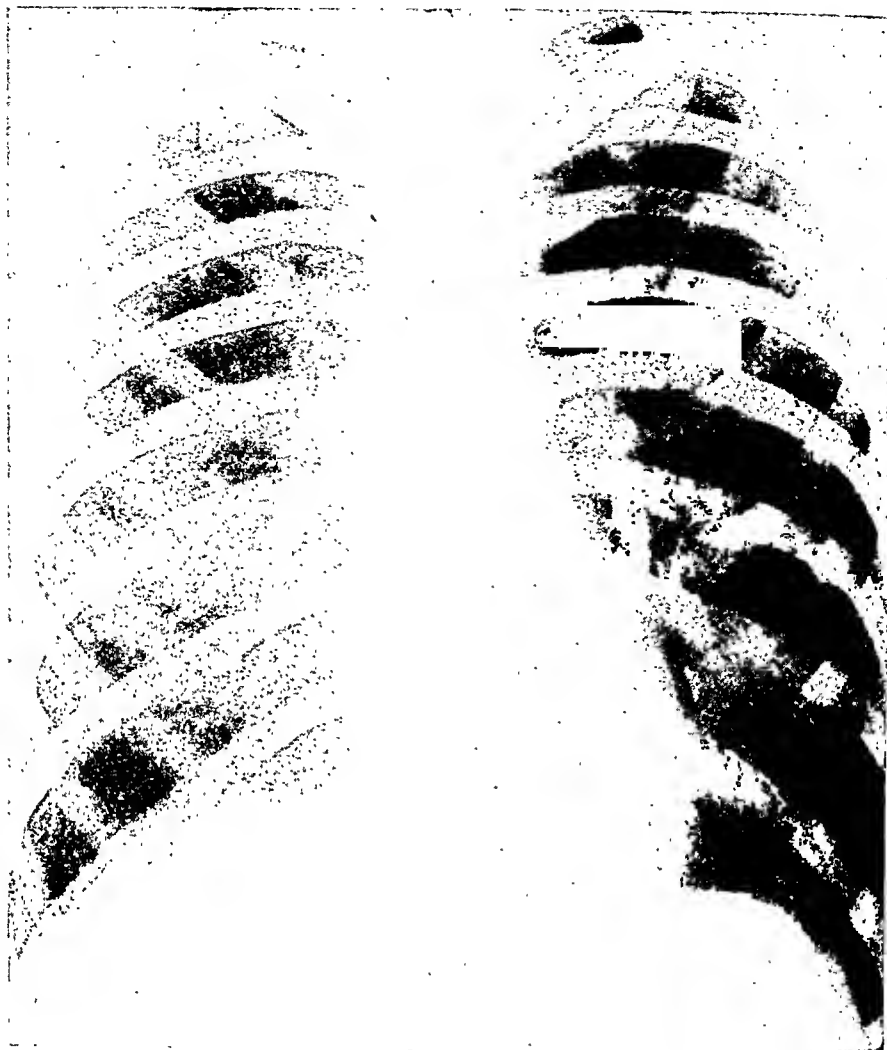


FIG. 5A.

other locations, it is contraindicated in such patients. A subpleural cavity presents the risk of tearing into the pleural space and causing spontaneous hydropneumothorax. The following illustrative case typifies this problem. A detailed history was sent us by Captain T. E. Finegan<sup>12</sup> who was associated with Captains R. Sleeter and C. S. McGill in the care of the patient at Madigan General Hospital.

A 26 year old white male lived in Pixley, California, in the heart of the coccidioid endemic area of the San Joaquin Valley from 1935-1942. He joined the Navy in 1942 and returned home from time to time. Because of cough, hemoptysis and considerable sputum while on sea duty in 1945, he was returned to the United States. In September 1945 he entered Corona Naval Hospital with the diagnosis of tuberculosis, pulmonary, reinfection, active, moderately advanced. He had a 2.4 cm. thin walled cavity in the periphery of his right lung at the level of his seventh dorsal vertebra. His sputum and gastric specimens were negative for *M. tuberculosis* and his sedimentation rate was only 10 mm. A serum specimen was sent us in No-

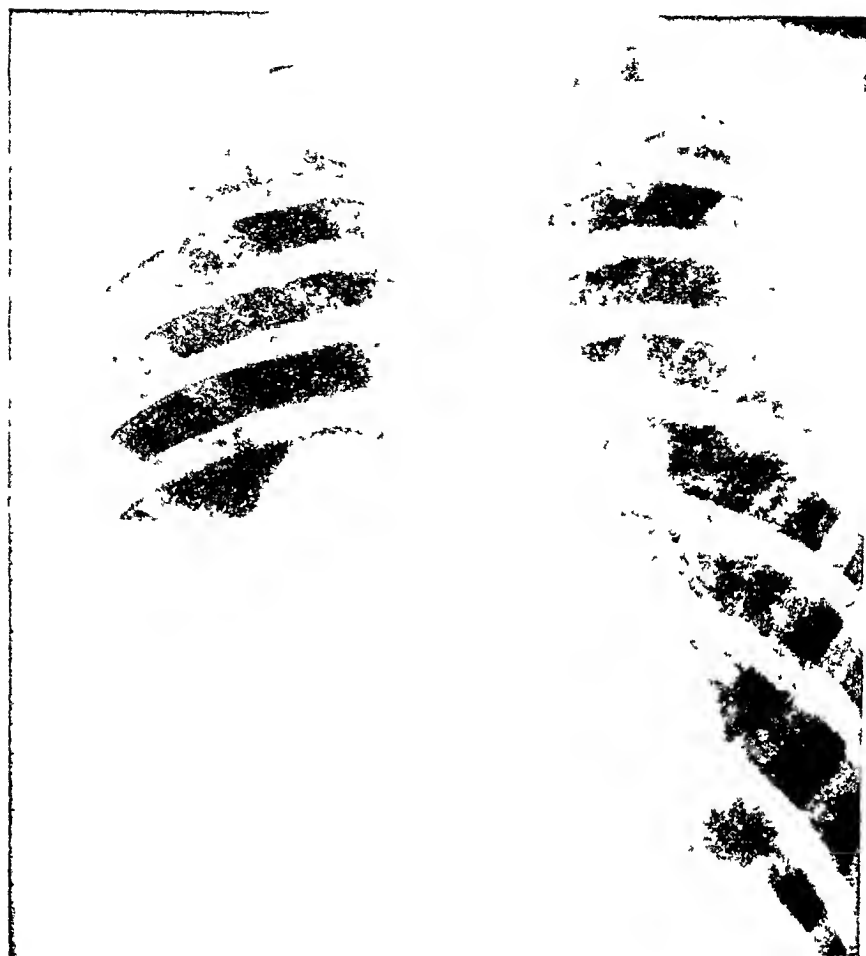


FIG. 5B.

vember and revealed complete fixation of complement through 1:4 dilution. His 1:100 coccidioidin was negative, as was his 1:1,000 tuberculin. We have no record of a 1:10 coccidioidin. He was discharged to the Veterans Administration and left the Los Angeles Veterans Administration Hospital in March 1946 with cavity still present after over six months of continuous hospitalization. In October 1946 he moved to the state of Washington. We received another serum specimen from him then which was identical with the initial one a year previous. He managed fairly well but tired easily. When fatigued, he coughed and raised considerable sputum which was frequently bloody.

On June 6, 1947, he developed a high fever, malaise and severe cough. He was treated by a private physician with penicillin and sulfonamides. His temperature dropped, but was still 101° F. in the afternoon for some time. The roentgenogram taken June 20, 1947 (figure 5A), shows the large thin walled peripheral cavity. On June 27, 1947, he was awakened by a very severe pain in his right chest followed by shortness of breath. He entered Madigan General Hospital the next day. A roentgenogram (figure 5B) confirmed the physical examination which revealed hydro-pneumothorax with fluid to the level of the sixth rib anteriorly. He was treated with bed rest and repeated thoracenteses with additional removal of air. As the series in figure 5 shows, the fluid level fell and the lung reexpanded, although not completely. As late as January 15, 1948, 500 c.c. of fluid were removed. The old



FIG. 5C.

cavity could not be seen. The patient felt quite well. A fungus recovered from the fluid by Lt. M. S. Heep was confirmed by us as *Coccidioides immitis*.

Seven or 2.6 per cent of the entire group of coccidioidal cavity patients developed spontaneous hydropneumothorax. As a complication of pneumothorax treatment, a bronchopleural fistula and pyopneumothorax occurred in an eighth. This patient had a pneumothorax for a "tuberculous" cavity but no tubercle bacilli had ever been demonstrated and *Coccidioides* was recovered from his empyema and sputum. We performed confirmatory studies on four other patients with spontaneous hydropneumothorax but whether there was antecedent cavitation is not known. Their histories indicated they were not undergoing primary coccidioidal infections at the time of the onsets of pneumothorax. However, during the course of clear-cut primary coccidioidal infections, spontaneous hydropneumothorax developed in three persons. One is included in the seven patients with known antecedent cavities. In the other two no cavity had been demonstrated. We saw another patient with repeated episodes of spontaneous pneumothorax shortly after his coccidioidal infection was acquired. They were incomplete

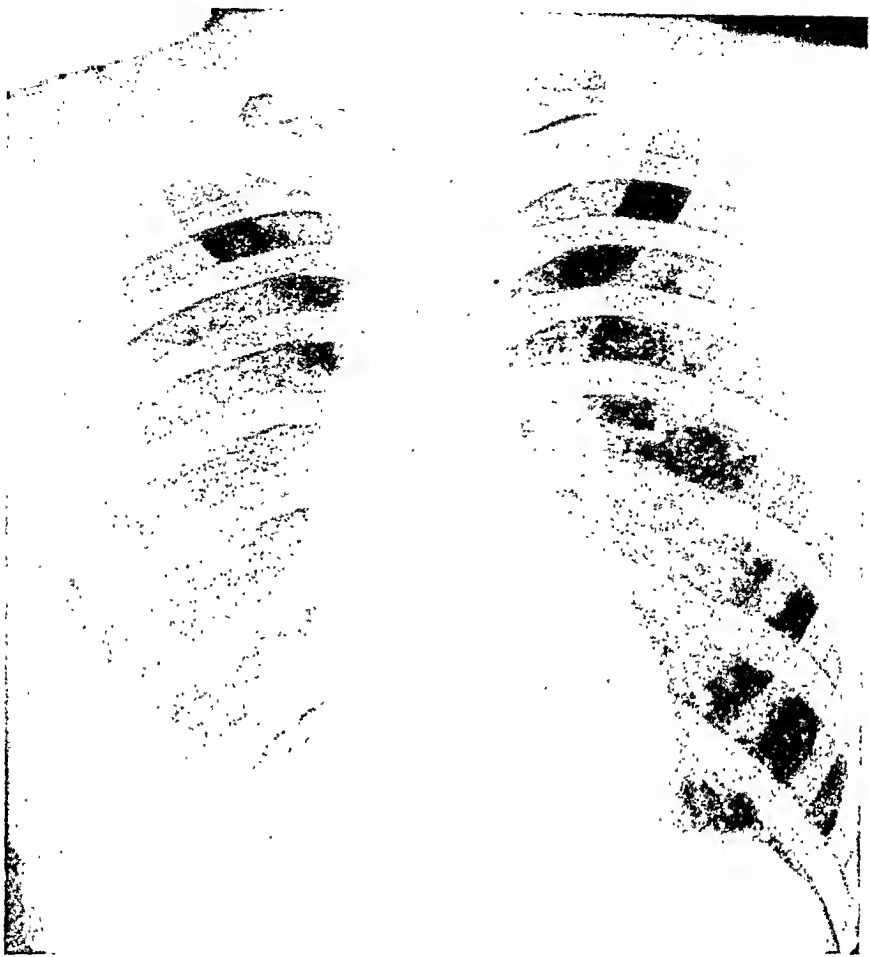


FIG. 5D.

and no fluid formed. However, this experience indicates that spontaneous hydropneumothorax can occur during initial infection without definite cavity formation. In one civilian and one soldier who underwent spontaneous hydropneumothorax during these acute initial infections, severe diabetes mellitus developed. Previous examinations of the soldier's urine established the association of the diabetes with the infection. The civilian had been circumcised under a general anesthetic only a month before and his preoperative urine examination revealed no sugar.

From the fluid of each of the 14 patients with coccidioidal hydro- or pyopneumothorax the fungus was recovered. In one<sup>29</sup> tubercle bacilli were also recovered. Thoracotomies with excision of the fistula and decortication were performed in four. Three of the four regained full lung expansion but in the fourth subsequent thoracoplasty was necessary to obliterate pleural space. The patient with post-pneumothorax empyema required intercostal skin-flap drainage and thoracoplasty. As in simple lobectomies and cavity resections, this more drastic surgery never resulted in disseminations or other coccidioidal complications.



FIG. 5E.

FIG. 5. Development of spontaneous hydropneumothorax as complication of peripherally located coccidioidal cavity. The series of roentgenograms was reproduced by Madigan General Hospital Photographic Laboratory and made available from files of the Army Medical Museum. For account of case see text.

A. Pre-admission roentgenogram seven days before spontaneous hydropneumothorax. Peripheral thin-walled cavity in right lung.

B. Admission roentgenogram two days after spontaneous hydropneumothorax showing collapsed lung, fluid and mediastinal shift.

C. Some expansion of lung and less fluid two months after spontaneous hydropneumothorax.

D. Progressive improvement three months after hydropneumothorax.

E. Continued reexpansion and small amount of fluid four months after hydropneumothorax.

However, seven months after spontaneous hydropneumothorax, lung was incompletely expanded and some fluid was present.

### SUMMARY AND CONCLUSIONS

Coccidioidal pulmonary cavitation may develop in an area of pneumonitis or in a residual lesion some months after the primary infection. Patients with cavities rarely disseminate their infections, appearing to possess an

effective immunity mechanism. Frequency of cavitation in inapparent coccidioidomycosis is not known. The cavitation incidence in Army hospitalized cases of coccidioidomycosis has ranged from 2 to 8 per cent.

Coccidioidal etiology of 274 pulmonary cavities was verified by recovery of the fungus in 40 per cent, positive serology in 49 per cent and positive coccidioidin and negative tuberculin in 11 per cent. Double infections, tuberculous and coccidioidal, were seen in seven of the group. In none was the coccidioidal infection progressive and in only one was tuberculosis progressive.

The relatively benign nature of these cavities is indicated by the fact that in the military patients three-fifths of the cavities were incidental discoveries and only two-fifths of the diagnoses resulted from symptoms. Among civilians nearly three-fifths of the initial roentgenograms were taken because of hemoptysis which, however, was rarely a real menace to health. The other signs and symptoms of tuberculosis were strikingly infrequent.

Ninety per cent of the cavities were single and 70 per cent were located in the upper chest.

A coccidioidin skin test is the first diagnostic step. Approximately 10 per cent may require coccidioidin stronger than 1:100. A few may be negative even to 1:10, but, misunderstanding in the interpretation of the skin tests frequently accounts for reported negatives. If antigenic strain variations occur, they are exceedingly infrequent.

Where serology is negative and the tuberculin test is positive, the diagnosis can be established only by recovering the fungus from sputum or gastric contents. In three-fifths of the sputum-positive patients with coccidioidal cavities proof of etiology could also be established serologically. When positive, fixation of complement was usually only to a low titer in distinction to the high titer characteristic of disseminated infection. Even while cavities were forming, decline in titer of complement fixation and slowing of sedimentation rates were noted. Three-quarters of the sedimentation rates reported to us were normal.

In treating cavities, one must realize that while many cavities close quickly, a considerable proportion may remain open for many years, rarely producing serious health problems. Bed rest doubtless aids in closing cavities early in their evolution, but has limited value later. The risk of dissemination being negligible and possibility of contagion very remote, drastic intervention should be reserved for specific indications. Phrenic interruption sometimes succeeds in closing even long established cavities. Pneumothorax may be used in selected cases but not with peripheral cavities because of the hazard of creating a bronchopleural fistula. Qualified thoracic surgeons have successfully performed many lobectomies, wedge resections and at least one simple excision of coccidioidal cavities. The high level of immunity in patients with cavities eliminates hazard of dissemination or even local extensions as long as bacterial infection is prevented.

Surgical removal of a persistent subpleural cavity may be undertaken to eliminate the hazard of spontaneous hydropneumothorax. Of 13 patients with coccidioidal spontaneous hydropneumothorax, seven were demonstrated to have had antecedent cavities. Thus spontaneous hydropneumothorax occurred in 2.6 per cent of our patients with coccidioidal cavities. Four were treated successfully by excision of the bronchopleural fistula and decortication. One other patient with cavity developed pyopneumothorax as a complication of pneumothorax treatment. Success of appropriate lung surgery and freedom from dissemination and local spread again were notable in these five surgically treated cases.

Coccidioidal cavitation and spontaneous hydropneumothorax, while admittedly undesirable, are much less hazardous than similar appearing tuberculous lesions and incomparably less dangerous than the disseminating coccidioidal granuloma.

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# THE TREATMENT OF ROCKY MOUNTAIN SPOTTED FEVER WITH CHLOROMYCETIN \*

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THE demonstrated efficacy of Chloromycetin in the treatment of human cases of scrub typhus<sup>1</sup> encouraged belief that this new antibiotic might likewise prove effective in the therapy of Rocky Mountain Spotted Fever. During the months of May, June, and July, 1948, a total of 17 cases with the clinical diagnosis of Rocky Mountain Spotted Fever were treated with Chloromycetin.† In 16 of these cases adequate confirmation of the clinical diagnosis was obtained through animal inoculation and serological tests. One of these cases was discarded because of the stage of the disease. The present report deals with the therapeutic results obtained in the remaining 15 proved cases.

Chloromycetin was originally prepared by Ehrlich and associates<sup>2</sup> from liquid cultures of a *Streptomyces* originally isolated by Burkholder‡ and shown by him to possess antibacterial activity. It is a crystalline substance relatively insoluble in water, but well absorbed from the gastrointestinal tract. In spite of its bitter taste it is well tolerated when given orally and serum levels of the drug after oral administration have been found to be parallel with those after parenteral injection. The toxicity of the drug is apparently low. When given intravenously in mice and intramuscularly in dogs,<sup>3</sup> Chloromycetin is well tolerated in single doses up to 100 mg./kilo body weight. Dogs injected intramuscularly twice daily with 36 to 44 mg./kilo of Chloromycetin for 24 days developed a moderately severe anemia, without significant changes in the white blood cells and without disturbance in hepatic or renal function. Since the Chloromycetin was in colloidal solution in 62 per cent propyleneglycol, it is not clear that the anemia can be attributed solely to the antibiotic.

Reports up to the present time on the therapeutic use of Chloromycetin orally in man have indicated the absence of any toxic manifestations. These reports, however, have dealt solely with Chloromycetin used over short periods up to 8 to 10 days. Whether the continued use of the drug in

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† The Chloromycetin used in this work was furnished by the Research Division of Parke Davis and Company.

‡ Dr. Paul R. Burkholder, Osborn Botanical Laboratory, Yale University.

humans for long periods of time would provoke toxic symptoms is as yet unknown.

The initial studies of the antibiotic spectrum of Chloromycetin in vitro and in vivo in animals indicated outstanding effectiveness in rickettsial infections of chick embryos and mice.<sup>3,4</sup> In human rickettsial infections Chloromycetin has demonstrated curative properties in scrub typhus fever<sup>1</sup> and in epidemic typhus.<sup>5,6</sup> It has also been shown to exert a specific therapeutic effect in typhoid fever.<sup>7</sup>

*Selection of Cases.* The Eastern form of Rocky Mountain Spotted Fever is endemic in Maryland. The common proved vector of the disease is the dog-tick, *Dermacentor variabilis*. The seasonal incidence of the disease begins usually in May, reaching its peak towards the end of June and falling rapidly in the later summer months. The annual total number of reported cases in this state has averaged 57.6 in the last 10 years. The majority of the cases occur in the Eastern half of the state.

Coöperation of practicing physicians in the affected counties resulted in the reference of a considerable proportion of the cases of Rocky Mountain Spotted Fever occurring during the period of this study, to the University Hospital in Baltimore. During this time 19 cases were so referred with the clinical diagnosis of Rocky Mountain Spotted Fever. Of these, two were not treated with Chloromycetin.\* In the remaining 17 cases the clinical diagnosis of the referring physician was concurred in and treatment instituted.

In one of these 17 cases laboratory confirmation of the diagnosis was not obtained. In this case the clinical response to the drug was prompt and favorable, but for the purpose of this report the case is excluded from consideration. In a second case, admitted on the twenty-first day of the disease, treatment was not begun until the twenty-second day and though this case was proved by positive agglutination and complement-fixation tests and showed characteristic drop in fever to normal during therapy with Chloromycetin, it has been excluded from the report because of the uncertainty at this late stage, as to whether the fall in fever should be attributed to the effect of the drug or to spontaneous abatement of the disease. There remained therefore the 15 cases, here reported, in which the clinical diagnosis of Rocky Mountain Spotted Fever was made and confirmed by later laboratory findings and which were treated with Chloromycetin and observed throughout the remainder of their febrile course and convalescence in the hospital. Ten of these patients were under 16 years of age (2 to 16) and five above this age (17 to 64). Seven were males and eight females. All were white.

\* In one case, a female child of 5, the clinical diagnosis was considered doubtful and there was an accompanying acute appendicitis with a leukocytosis of 20,000. The second case, an infant of 4, was brought into the Accident Room in extremis and died there in three hours.

*Diagnostic Criteria. A. Clinical.* In the establishment of the clinical diagnosis the following factors in the history and examination were considered of primary importance:

a. History of exposure to ticks and of tick bite. All 15 cases gave a history of exposure to ticks and 12 a history of the removal of an attached tick within the two weeks preceding the onset of their febrile disease.

b. Persistent fever since the day of onset. In all cases the history indicated that fever had been present daily from the date of onset until admission. In 11 cases the patient was observed in the hospital over a period of from 24 to 72 hours prior to administration of specific therapy and the presence of continued fever confirmed. In four cases the severity of the patients' illness precluded this period of observation.

c. Characteristic rash. In all cases a rash, characteristic both as to individual lesions and as to distribution, was observed prior to the initiation of specific therapy. In a number of cases the rash was considered only suggestive on admission but became fully characteristic during the period of observation prior to therapy.

d. Secondary clinical features. When present the following symptoms and signs were considered to favor the diagnosis of Rocky Mountain Spotted Fever: prominence of headache, mental dullness, torpor or delirium, palpable spleen (especially in children), tarsal conjunctivitis, slight periorbital edema and photophobia.

e. Absence of evidence by history, physical examination and laboratory tests of other infectious disease. No evidence of another type of infection capable of producing the clinical picture was found in any case. Blood cultures were made in each case and were uniformly negative.

*B. Laboratory.\** Confirmation of the clinical diagnosis of Rocky Mountain Spotted Fever was sought in each instance through the following procedures:

a. Blood was drawn prior to the initiation of Chloromycetin therapy and, an average, of four times during therapy. From each blood sample two male guinea pigs of approximately 250 grams were injected intraperitoneally with 4 c.c. of suspended blood cells. The initial blood sample of 8 to 10 c.c. was allowed to clot in an incubator, the serum decanted, the remaining clot ground up in 8 to 10 c.c. of saline solution and the total then divided into two portions for injection. Temperatures of all guinea pigs were taken daily for 21 days. A rise of temperature above 104° F. over three consecutive days or more was considered positive indication of transmission, if later confirmed by complement-fixation in the guinea pigs' serum. In the present study a positive complement-fixation was obtained from the blood of all pigs showing a positive febrile response.

\* Grateful acknowledgment is made to the following laboratories which performed the serological tests: Department of Clinical Pathology, University Hospital, Baltimore, Md.; The Department of Virus and Rickettsial Diseases, Army Medical Center, Washington, D. C.; Maryland State Department of Health.

b. Agglutination tests for *Proteus* OX19 were performed in all cases prior to the administration of Chloromycetin and thereafter approximately every four days while in the hospital. In some instances blood was obtained at irregular intervals after discharge of the patient. Agglutination titers higher than 1:160 were considered positive.

c. Complement-fixation tests. Each patient's blood was tested for complement-fixation against the antigen of *Rickettsia (Dermacentroxenus) rickettsi* prior to therapy and whenever blood was drawn for agglutination test thereafter. Complement-fixation with titers of 1:10 or higher were accepted as positive.

In evaluating results of laboratory diagnostic procedures in individual cases, a strongly positive reaction in any one of the three categories, that is animal inoculation, agglutination of OX19, or complement-fixation, was accepted as adequate confirmation of the clinical diagnosis.

In the 15 cases which constitute this series, six gave positive results by all three methods, eight gave positive reactions by two tests and one by one test only. There were seven cases in which guinea pig inoculation proved positive; 14 cases gave positive agglutination tests; and 15 positive complement-fixation reactions.

#### SPECIFIC THERAPY WITH CHLOROMYCETIN

a. Method of administration. Chloromycetin, furnished by the research division of Parke Davis and Company for the purposes of this experimental study, was in the form of 0.25 gm. tablets. These were administered orally. In adults and in many children whole tablets were swallowed. In general in spite of the bitter taste of the drug, surprisingly little difficulty was experienced with oral administration. In some young children the tablets were pulverized and suspended in water or in dilute chocolate syrup, or given in gelatin capsules. In one instance it was necessary to administer the drug by gavage. Vomiting of the drug on initial administration occurred in two or three cases, but was satisfactorily handled by one or another of the methods mentioned above.

b. Dosage. The dosage regime adopted was empirical, being based in general, however, on doses reported as effective in scrub-typhus fever. Following a large initial dose the drug was given on a three hour schedule. In the first four cases therapy was continued for four days after the temperature reached permanent normal levels. In the remaining cases the policy was adopted of discontinuing the drug when the temperature had remained below 100° F. (rectally) for 24 hours.

The initial dosage was 50 mg./kilo in cases 1 and 2 of the series. Thereafter it was raised to approximately 75 mg./kilo of estimated weight. In case 11 in which gavage had to be employed, an initial dose of 128 mg./kilo was administered. The initial dose was usually administered in two or three parts at approximately one hour intervals.

After the initial dosage the drug was given at three hour intervals day and night. Arbitrary dosages employed were 0.25 gm. every three hours for children under 16 years of age (10 cases), and 0.5 gm. for those above this age.

### THERAPEUTIC EFFECTS OF CHLOROMYCETIN TREATMENT

a. Clinical status. Improvement in patients' symptoms was uniformly observable but not striking in the first 24 hours. However, on the second day of treatment abatement of such symptoms as headache, mental dullness, etc., was definite. The eruption did not spread following initiation of treatment and by the end of the second day had markedly receded. On the third day, in the majority of cases, the patient was plainly convalescent with interest in his surroundings, increased strength, return of appetite and freedom from symptoms.

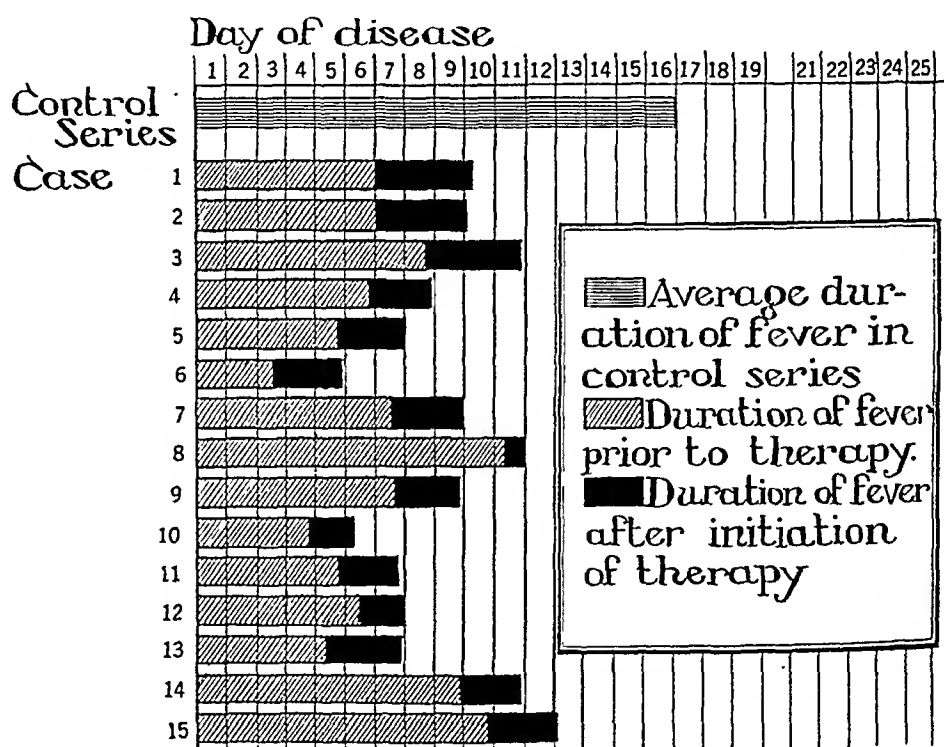


FIG. 1. Duration of fever in 15 cases of Rocky Mountain Spotted Fever treated with Chloromycetin contrasted with average duration of fever in a control series of 46 cases.

b. Fever. The recorded data as to the effect on the febrile course constitute the most striking evidence of the therapeutic effectiveness of Chloromycetin in this disease. Irrespective of the height of the preceding fever or the age of the patient, Chloromycetin therapy was followed in all cases by fall of temperature to normal levels within 76 hours (figure 1) after the initial dose. The average duration of fever after initiation of therapy was considerably less, approximately 2.2 days.

Temperatures were taken rectally at four hour intervals day and night in these patients. Normal temperature level was defined as rectal temperature remaining under 100° F.

In no instance after normal temperature had been reached and remained normal for 24 hours was there any secondary rise which might be interpreted as a relapse; nor did fever appear during convalescence, suggestive of a recurrence of the disease.

c. Rickettsiemia. In the seven cases in which the guinea pig inoculations from blood taken prior to the initiation of therapy proved positive, inoculation of further guinea pigs with the same patient's blood taken after the initiation of therapy, yielded no febrile response in the guinea pigs. In each of the seven cases blood was drawn two to four times on successive days beginning with the second day of treatment and two guinea pigs inoculated on each occasion. A total of 34 guinea pigs were thus utilized.

These negative findings suggest that rickettsiemia disappears rapidly after the initiation of Chloromycetin therapy. However, the possibility is not covered that some of these pigs might have acquired an inapparent infection which would be detected only by complement-fixation tests on their blood. Further work and a larger series will be required to settle this point.

d. Development of immune bodies. Increasing titer of agglutinins for *Proteus* OX19 and of complement-fixing antibodies was observed in these 15 patients during convalescence following Chloromycetin therapy. It would appear that the premature termination of the active disease by Chloromycetin does not alter the usual course of development of these immune bodies.

e. Convalescence. From the clinical point of view convalescence of these cases proceeded in normal fashion. It was proportionate in length to the severity and duration of the initial febrile period of the disease.

*Evidences of Toxicity of the Drug.* Mention has been made of the fact that on initiation of therapy vomiting of the first or second dose occurred in a few cases. In no instance, however, did vomiting persist. It was our impression that psychic factors as well as the bitter taste were responsible for such vomiting as occurred. No diarrhea or jaundice was observed. Repeated urine examinations showed no evidence of significant albuminuria, casts or crystals. Analysis of the blood counts during and after treatment showed no striking variations from their original levels.

#### COMPARISON WITH CONTROL SERIES

In order to be able to compare the Chloromycetin treated cases with a series of cases of Rocky Mountain Spotted Fever which did not receive any specific chemotherapeutic agent, an analysis was made of the records of 46 cases of this disease admitted to the University Hospital prior to availability of para-aminobenzoic acid therapy or Chloromycetin. In figure 2 is shown graphically the day of disease on which the febrile course in each of these 46

cases terminated. It is evident that the natural course of the fever in this disease usually terminates between the thirteenth and the twenty-first day of the illness. The average duration of fever in these 46 cases was 16.04 days. These 46 cases comprise the total number of cases, admitted during the period 1930 to 1946, which recovered and which showed no complications that might have prolonged their febrile course.

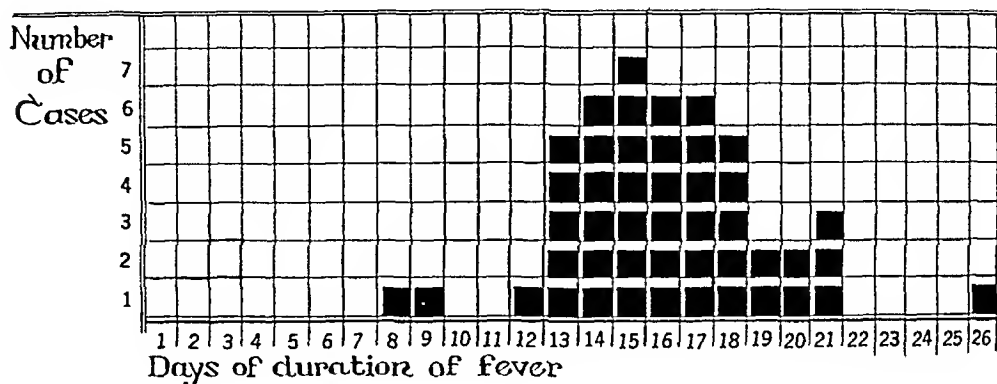


FIG. 2. Duration of fever in 46 non-fatal cases of Rocky Mountain Spotted Fever in Maryland which did not receive specific therapy. Cases with complications which might prolong fever were excluded. Black squares indicate day of disease on which fever terminated.

In contrast figure 1 indicates the day of the disease on which fever terminated in each of the 15 cases treated with Chloromycetin. The uniform shortening of the duration of the febrile course as a result of therapy is plainly evident.

Statistics of the Maryland State Department of Health show that 576 cases of Rocky Mountain Spotted Fever were reported in the years 1938 to 1947 inclusive. The number of deaths for this period was 120, giving a mortality rate of 20.8 per cent. In the Chloromycetin series there was no mortality. Among the 15 cases of this series four were classed clinically as virulent forms of the disease.

### DISCUSSION

It is considered that the evidence presented indicates that the new antibiotic Chloromycetin, in addition to its previously demonstrated effectiveness in the treatment in man of scrub typhus and of epidemic typhus is also an equally effective agent in the treatment of Rocky Mountain Spotted Fever. Further studies will be required to determine whether murine typhus, Q fever, and other members of the family of rickettsial diseases will yield in similar fashion to this therapeutic agent.

The question of the proper dosage of the drug and particularly the number of days during which its administration should be continued, is still undetermined. In the present relatively small series of cases no instance of

recurrence of the disease was observed when the drug was discontinued after 24 hours of normal temperature. This schedule was employed for investigative purposes and because of the scant information as yet available bearing on possible toxic effects of long continued administration. A very much larger experience with the use of Chloromycetin in Rocky Mountain Spotted Fever is required to demonstrate whether such a brief course of treatment is adequate to eliminate completely the rickettsial infection. The occurrence in animals of inapparent infections and the suggestive evidence, indicating that Brill's disease in humans is due to the recrudescence of a latent rickettsial infection, both point to the possibility that incomplete therapy might be followed by a latent form of Rocky Mountain Spotted Fever.

### CONCLUSIONS

The results of treatment of 15 cases of Rocky Mountain Spotted Fever with the antibiotic Chloromycetin indicate that this drug is an effective therapeutic agent in this disease.

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## PSYCHOANALYSIS \*

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MODERN psychiatry is based on the fundamental contributions of three men. Cannon intensely studied the physiological manifestations and ramifications of emotions. Pavlov conducted ingenious research on the nervous system integrations involved in the process of learning, habit formation, and conditioning. Freud traced the origins of many neurotic illnesses to childhood and infantile experiences and investigated the complex conditionings of the individual in his family life. These conditionings he believed in many instances established the predisposition to neurosis and psychosis.

The family is the primal social relationship. In the interactions of parents and children in the family setting, infants and children experience feelings which are most important in the development of the personality. Feelings and emotions are the heart of the personality. Experiences determine or condition feelings. Persons in the family by their attitudes and behavior induce and establish feelings that are often characteristic of an individual for life, frequently determining his success or failure and his health or morbidity.

Parents or their surrogates in their contacts and handling of even very young children can produce four general groups of feelings. 1. Security and well-being. 2. Insecurity and fear. 3. Irritation, anger, temper. 4. Tension, uncertainty, worry, and depression.

Security and well-being are given by experience of warmth, gentleness, tenderness, support, care, dependability, ministrations to and satisfactions of basic needs, and love. Insecurity and fear are stimulated by delay and deferment of basic gratifications, aloneness, lack of care, deprivation, and rejection. Irritation and anger are aroused by discomfort, impatience, roughness, lack of satisfaction of soothing stimuli, forcing, and frustration. Worry and depression are excited by irregularity, uncertainty, inconsistency, indifference, neglect, and deprecation.

The early expression of tensions, unsatisfied hungers, fear, overstimulation, and anger is in crying. These emotions are, early, not always clearly differentiated, and find common pathways of expression in unorganized hyperactivity of the skeletal musculature and crying. The various bodily systems, such as the respiratory, circulatory, gastrointestinal, and urinary systems, participate vigorously in these reactions. Later the emotions of fear, anger, and depression become differentiated by stimuli, organization, thought content, and type of activity. All of these involve intense physiological disturbances. Crying of course drops out except in unusually intense situa-

\* Delivered at the Regional Meeting of the American College of Physicians, November 21, 1947.

From the Institute of the Pennsylvania Hospital.

tions. But intense physiological disturbances within, remain as the chief outlet or expression of emotions. These physiological disturbances acquire a pattern through repetition that is often characteristic of an individual. The physiological manifestations in characteristic form for a given individual form a sort of body language or organ language. Thus nausea may be the expression of dissatisfaction or disgust; diarrhea of insecurity and worry; colitis and migraine of anger; tachycardia and palpitation of fear; and constipation of restraint, resistance, and stubbornness. This organ or body language constitutes the so-called *organ neuroses* or *neurasthenia*. The intensity and emphasis of the physiological responses make them more apparent and important than their psychological content.

A sort of law might be formulated. Early in life physiology expresses what is later psychology. Later in life psychology (attitudes, thoughts, feelings) often uses early patterns of physiology to express itself.

The successful, mature adult must have the following characteristics. He must be secure, independent, take responsibility, coöperate with others, be able to tackle and to solve problems, and love or be devoted to persons, things, activities, movements, institutions, or causes, beyond himself.

Security and self-confidence are necessary to approach the new, to meet changes, to stand alone. Courage is necessary to tackle uncertainties. Confidence and courage are required to develop independence; to make decisions, become decisive, and self-directing (i.e., not too dependent). The effective adult must be able to take responsibility. He must act on his own initiative, develop plans, and organize his activities. He must carry through, be reliable and accountable. The mature person is able to coöperate with others. He can work, apply his skill, exert effort, and persevere. The successful adult must be able to meet problems, uncertainties, mistakes, frustrations, disappointments, rejections, limitations, deprecation, unfairness and meet them constructively. That is, he must meet such circumstances without developing unusual or handicapping bodily discomforts or intense emotionalism. If these make one unhappy or ineffective, his condition is called a psychoneurosis. If they are so intense that the individual is unable to work or get along with his fellows (with elated, depressed, paranoid, or schizophrenic mechanisms), the state is called psychotic. In both of these states the old incoördinations of childhood (psychoneuroses) or infancy (psychoses) are reawakened and expressed in musculo-skeletal, visceral, and intense emotional reactions. This reawakening or return to former, older patterns of response is called *regression*.

The infant and young child are constituted essentially of physiology, instinctual feelings, and actions. With cortical development, physiological and instinctual-emotional energies become channelized and organized into patterns of effective neuromuscular actions, under the acquisition of skills, socially approved goals, and conditioning or training. Defective, traumatic, unwise conditioning and frequent physical disease interfere with effective organization and development. Severity of these handicaps (too much ex-

perience of lack of well-being, fear, tension, anger, etc., in the early home environment) and chances of development determine whether the individual will develop as: 1. a rugged, normal personality; 2. an apparently normal person with, however, instability and a tendency toward regression; 3. a person with obvious handicaps such as dependency, or lack of initiative and aggression; 4. a person thrown back into regressive physiological reactions such as conversion hysteria, neurasthenia or hypochondriasis; 5. one with intense exaggerated emotion as in anxiety hysteria or obsessional neurosis; 6. or one with completely disorganized patterns such as manic-depression and schizophrenia. Thus an individual becomes a thalamic, emotional, viscerally organized person with the typical expressions, instead of one with a cortico-skeletally patterned organization. The training the child receives, his conditioning, determines whether adult adequacy, defective development, or instability and readiness to regress to thalamic responsiveness, result.

The family is the place where organization and control are developed or susceptibility to disorganization and decontrol. The family, as has been said, is the basic social relationship. Here the child feels and experiences security, warmth, love, well-being, according as he is handled, or insecurity, fear, aloneness, tension, irritation, and anger. Unwise love, devotion, attention, protection, supervision, induce dependency, insecurity, fear, inferiority, lack of initiative, self-confidence, and courage. Not enough warmth, fondling, and tenderness lead to unresponsiveness, coldness, aloneness, and insecurity—the forerunners of schizophrenia. Bottle-fed babies, uncuddled, on rigid routines, with no concessions to human feelings, lead to feelings of isolation and rejection, which ultimately appear as the utter aloneness and seclusiveness of the schizophrenic patient. Too much control, suppression, domination, supervision, regimentation, and punishment leave the child devoid of personality, with doubt and indecision, or too much anger and revolt.

It is a question of balance. There should be enough love, devotion, and protection for security, but not too much to retard independence and growth. There should be sufficient direction and supervision, so the child obtains enough support to try new things, develop self-confidence, and initiative; but not too much to prevent the development of independent decision and self-direction. There should be enough discipline to learn the nature of the world—especially the social world with its expectations and demands; but not too much to produce crippling fear, resentment, or rebellion.

In the family, with the mother, father, and siblings, we learn to share, yield, postpone satisfaction, tolerate, coöperate and contribute. The child finds it difficult to share his clinging, dependent love (security) with his father (frustration, deprivation, discipline, punishment). In this emotional relationship, intense feelings are mobilized, of increased love—dependency demands (as compensations for loss and threat of loss); insecurity and fear, irritation, anger and hostility, envy, jealousy and guilt. The feelings of

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security, warmth, and well-being, or of anxiety, tension, and hostility, aroused in relation to parental handling of the child, parental attitudes toward one another and toward the child—this vast complex of feeling relationships is what Freud meant by the *Oedipus Complex*. Rejection of the child by attitudes or subtly expressed feelings, undue lack of consideration for the child's needs and helplessness, undue deprivation, postponement of satisfactions, frustration, sternness, exactitude of toilet training, e.g., threats of or actual punishment—acts or attitudes that devitalize, that take away the normal power and adequacy of the child, or that deprecate his personality, and the associated feeling reactions of fear, envy, jealousy, resentment, hostility, discouragement, and inferiority, are what is meant by the *Castration Complex*.

On the resolution of these vast complicated complexes of feelings in the family relationship will depend the future stability of the personality or the predisposition to emotional (i.e., nervous or mental) illness. If the parent gives the proper amount of love, tenderness, support, guidance, and control—and not too much or too little—a child will not be unduly emotional, with its physiological counterparts. He will be able to defer, tolerate discomfort and tension, postpone satisfaction, share, coöperate, and contribute. His intellectual development will proceed normally, free to learn and apply skills appropriate to his age.

If the emotions are not guided, and conditioned wholesomely, the personality will be too emotional. The adult will have anxieties like the child who is insecure and fears being alone, or he will be phobic, like the child with panics at the sound of thunder or the sight of terrifying animals, or the adult will have hostilities and destructiveness like the tantrums of the child or depression like the rejected, deprecated, unprotected or overdominated child.

Psychoanalysis speaks of *fixation* when in infancy or childhood these emotions (love, parental dependency, fear, anger, depression) are excessively stimulated, so that in later life in the face of difficulties, unfair practices of others, situations requiring unusual effort and problems, old emotional thalamic patterns are revived and the patient regresses to the earlier, ineffective, unorganized, emotional reactions of early life. This is the meaning psychologically and developmentally of neurosis and psychosis. Just as in the decorticated animal there asserts itself overactivity of more primitive centers in decerebrate rigidity; so when the individual is psychologically overwhelmed or cortically disorganized, more primitive forms of emotional reaction appear.

Psychoanalysis has developed the concept of the *unconscious*. This is not a mysterious concept. It refers to phenomena where there is splitting, disconnection, or dissociation of processes that normally should be connected. It is lack of awareness of psychological (or conditioned) connections or relationships. For example, a patient said she had no temper or anger, yet had fears and impulses to break things. She did not recognize

the motivation or causes. She was not aware that the impulses to break things were related to her dissatisfactions and irritations (anger which she did not realize) with her husband. The things she felt like destroying were substitutes for the feelings toward her husband. There was here *substitution* of object and *displacement* of feelings. Similarly a woman had persistent, intractable, crippling pain in her back for several years. It was not relieved by orthopedic treatment. She was not aware that the pain was a displacement (conversion) of anger at her husband into muscle pain. These mechanisms of substitution, displacement, disconnection or *dissociation*, with lack of recognition of essential and causal relationships which are subsumed under the concept of the unconscious, make patients' reactions seem so often bizarre, unreasonable, and helpless before the ordinary processes of reasoning and will power.

The world of the neurotic and psychotic is personalized with the feelings and reactions that were directed as a child toward the parents in the family. That is why their reactions are so intense and personal. Psychoanalysis speaks of this process as *transference*. This is one explanation for the extraordinary devotion of patients toward doctors, and also patients' unreasonable bitterness and lack of coöperation.

In infancy and childhood, nutritive and eliminative satisfactions and discomforts with their physiological processes are dependent on the consideration, attitudes, and behavior of adults. The satisfaction of physiological hunger becomes equated with love, warmth, friendliness, and well-being. If there is a deficit of these psychological factors in infancy and childhood, there are often disturbances of the gastrointestinal functions. Later in life in the face of insecurity, difficulties, unfair consideration by others, deprivation, hostility and anger, the gastrointestinal functions will be disturbed and we call it a gastrointestinal neurosis. These functions have been sensitized in childhood by parental handling and discipline. In later life they are a more sensitive barometer to situations involving insecurity, deprecation, and frustration than the cortex. There will often be marked physiological disturbances by these factors before the individual is aware of the factors provoking the response. He is unconscious of them. It is as if the cortex is by-passed.

Another example may be given. Unusual exactitude in the demands of the parents in toilet training, precociously required before even cortical development of well coördinated muscular control has appeared, often has deleterious echoes in later life. It focuses undue attention (and stimulation) on the lower gastrointestinal tract. Parental pressure also creates resistance, resentment, hostility, and rebellion. In later life, in relationships or circumstances where people are normally demanding, dictating, controlling and frustrating, the former hostility and rebellion will be awakened. Such people have been conditioned, made sensitive or allergic to such recurrent situations. Again the lower bowel may be the first indicator or barometer of such relations. Disturbances of lower bowel function appear long be-

fore the patient is aware of the source of the difficulties. "Neurogenic" colitis may be appearing as the chief manifestation of resentment and anger. The personality and physiological organization of such individuals is what Freud meant when he spoke of an *anal character* or personality.

Hysterical characters are emotionally labile, with marked tendencies toward changeability, instability, reversibility, and increased predisposition toward physiological expression of emotions. A father was inconsistent. One minute he was adoring and indulging; the next minute he was dominating, punitive, rejecting, overwhelming, and hurting. The child's love, security, and creative impulses could not be organized. She was afraid the adoring one would suddenly change to the threatening one. So she had abnormal variations and fluctuations of fears, enthusiasms, loves, hates, depressions, and revolts. She was unable to move into a reasonably constant, loving, sharing, coöperating, contributing relationship with people. She could not become an adult psychologically because of the fixations or pressures forced on her by parental handling.

Psychoneurotic, psychosomatic (I prefer the term: functional medical conditions) and psychotic reactions, therefore, depend on or really are the expressions of the basic emotions of love and security, insecurity and fear, anger and hostility, and depression,—overwhelmingly conditioned, hyperstimulated, or inadequately expressed—in all their permutations, combinations, and distortions.

Life consists of a succession of circumstances where one must: make an effort, postpone or give up; attack or avoid; assert or submit; acquiesce or resist; dominate or defer; fight or withdraw; master or be defeated; express or restrain; survive or be destroyed; take or give; and other polarities. The resolution of these alternatives will depend on the basic thalamic instinctive organization or conditioning of the personality: the intensity and adequacy of our love-security, insecurity-fear, resentment-hostility, expansive-depressive make-up. The balance will be turned by the nature of these thalamic forces within us, more than by our cortex or reason. This organization is ultimately dependent, of course, on our heredity, physiology, and temperament, but functionally on the nature and the effect of parental conditioning of the child in the family situation—the results of the Oedipus and castration complexes in psychoanalytic terminology.

Sex, according to Freud, is popularly misunderstood. He broadened the concept. It is not limited in his conceptions to localized genital anatomy and genital function. Under sex he includes what most people think of by the words: love, interest, attraction, devotion, creativity, and the feelings and impulses related thereto, whether toward persons, money, causes, or scientific, literary, artistic, or social endeavors.

Therapy in psychoanalysis is devoted chiefly to relieving patients of crippling emotional tensions or hyperstimulations, and developing the patient's understanding of his pattern of personality organization and his

typical reactions to life situations. This is done chiefly through the process of free association, abreaction, and the interpretation of dreams and symptoms. *Free association* merely means talking of whatever comes to mind, and not having the content of the patient's remarks become directed by questions of the doctor. The latter is directed, controlled thinking. Free association expresses thoughts that come to mind however sporadic, unconnected, illogical, bizarre, or anti-social. By this process a sort of emotional gravitational trend of thoughts and attitudes comes into play and becomes apparent. The pattern of reaction becomes clear, as also its origin. That is the way one breaks through the irrational defenses and unreasonableness; whose source is not known to the patient. The rationality of symptoms becomes clear. The play of free association, of the apparently irrelevant, ultimately shows, to the patient, a logic beneath his symptoms, which is convincing.

In the play of free association there is frequently intense expression of violent emotion. This is called abreaction. It releases the patient from the crippling intensity of feelings, minimizes and desensitizes them. The unexpected intensity often focuses the patient's attention on relevant factors of which he had no awareness.

The insights and contributions of Freud have been epochal. Before his time psychiatry was classificatory, and treatment was expectant and custodial. Since his discoveries psychiatry has become etiological and dynamic, and therapy rational and psychological. His scheme of the development of the human personality has given us a paradigm by which we can understand much of the irrational, chaotic, and bizarre, seen in psychiatric conditions. Freud himself changed his formulations and that process is still going on with progressive thinkers in psychoanalysis.

Many patients, of course, cannot be analyzed—the majority of them for many reasons. But psychoanalytic insights are helpful in many conditions that cannot be analyzed. The psychoneuroses, some psychoses, and some psychosomatic or functional medical conditions, are those in which it may be employed.

The insights of psychoanalysis far transcend its therapeutic efficacy. The contribution of psychoanalysis as a method of investigating the human personality, as a tool of research, and as a means of insight, may very well turn out to be greater than as a method of therapy. But Freud's contribution has been basic and epochal in psychiatry. It has thrown light where there was darkness and confusion, and has brought order where we saw only chaos. It is like the introduction of the benzene ring in organic chemistry. It has made our thinking functional and dynamic rather than static and verbal. It has opened new realms in psychotherapy and made it rational. The extravagances and errors of observation and theory will be corrected by time and experience.



## ESSENTIAL FAMILIAL HYPERCHOLESTEROLEMIA \*

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THE metabolic disorder characterized by an increase of the total blood cholesterol with normal proportion of esters, and frequently an increase in the phospholipids, is designated by us as essential familial hypercholesterolemia. While this term does not follow the classifications proposed by Thannhauser,<sup>1,2</sup> Montgomery,<sup>3,4</sup> and others,<sup>5,33,31</sup> it is more descriptive and useful.

While many pathological conditions have been known to be associated with xanthomatous deposits in the skin, the significance of the primary metabolic disorder has not been fully recognized. Too much emphasis has been placed on xanthoma tuberosum, xanthoma tendinosum, and xanthelasma.

We were presented with a unique opportunity for the study of a familial condition. Not only were there four generations composed of 282 individuals available for investigation, but the various sibships were large and coöperative. Thorough clinical studies in 159 of these are used for statistical analysis. This group of 159 includes all individuals found to have elevated blood cholesterol, and many others with normal levels. The examinations are sufficiently complete to exclude the more common causes of hypercholesterolemia, such as nephrotic syndrome, diabetes, hypothyroidism, pregnancy, jaundice, and disease of the liver.

Our study included:

1. Medical history and physical examinations (rectal examinations were made only when suggested by the history; no vaginal examinations were done).
2. Urine was examined for albumin, sugar and urobilinogen. The sediment was examined if there was any albumin present.
3. Electrocardiograms were done on 21 of the group that had elevated blood cholesterol and on 11 of the normals.
4. Basal metabolic rates were determined if there was any suggestion of hypothyroidism.
5. Diet diaries were kept for a period of time. The results were analysed by competent dietitians and calculations of the cholesterol intake were made on 91 individuals.

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TABLE I  
Blood Lipid Values

Individual	Age as of March 1947	Total Cholesterol	Cholesterol Esters	Phospholipids	Total Lipids
A-1	30	335	262	260	865
A-1x	26	210	152	183	579
A-2	29	355	230	283	870
A-2x	32	180	107		
A-3	25†				1383**
A-4	23†				1330**
A-5	23	335	209	265	770
A-5x	27	208		248	
A-6	22	213	105		
A-8	19	216	120		
A-9	25	325	280	184	631
A-6x	25	262	250		
A-12	14	254	171	195	482
A-13	12	394	281	312	807
A-14	11	700	505	413	1350
A-16	8	185	110	217	
A-17	3	550	537	357	756
A-18	1	381	281	325	645
A-4x	35	250	166		
A-9x	25	250	125		
B-1x	62	237			
B-2	53	194*	135	235	699
B-2x	52	229	140		
B-3	51	187	135		
B-3x	49	141	100		
B-4	50	216	160	320	727
B-5	47	262	156		
B-9	46	300	102		
B-6	43	217	122		
B-6x	36	200	122		
B-7	41	183	112		
B-7x	35	251	105		
B-8	38	370	254	245	759
B-8x	36	150	67	163	510
B-10	49	446	382	300	937
C-1	49	288*	204	291	869
C-12	59	248	142		
C-12x	58	175	110		
C-11	56	350	205	330	
C-11x	59	230	136	145	679
C-10	57	320	210	423	1086
C-9	56	210	130		
C-8	53	196	127		
C-8x	57	210	170	255	
C-7	51	153	98		
C-7x	49	225	175		
C-4	48	182	117		
C-5	44	412	285	520	1516
C-6	42	146	83		
C-6x	42	175	116		
C-3	40	420	350		
E-3	71	400	162	360	1000
G-1	80	161	98		
G-4	77	212	120		
H-1	31	196	141		
H-2	30	186	108		
H-2x	28	187	87		
H-3	29	312	162		
H-1	28	166	89		

TABLE I—*Continued*

Individual	Age as of March 1947	Total Cholesterol	Cholesterol Esters	Phospholipids	Total Lipids
H-1x	30	200	117		
I-2	28	251	112		
I-2x	28	220	135		
I-5	25	205	130		
I-6	22	126	80		
I-3	17	215	127		
K-1	30	180	147		
K-1x	35	223	153		
K-2	19	248*	181		
K-3	25	140	80		
K-4	20	283	131		
L-2	22	237	140		
L-7	10	158	98		
L-9	7	160	78		
L-8	7	166	93		
L-12	3	200	180		
L-10	2	187	93		
BA-1	17	201	123		
BB-1	14	215	120		
BB-2	13	251	103		
BB-3	9	251	110		
BB-4	7	220	140		
BB-5	5	237	100		
BC-1	10	271	141		
BD-2	6	190	99		
BD-3	4	425	287	445	1328
BD-4	3	187	93		
BE-1	7	187	112		
BE-2	4	237	170		
BF-1	4	415	218		
BG-1	4	316	175	258	975
BI-1	32	147	107		
BI-4	29	152	90		
BI-2	28	205	100		
BI-3	25	135	100		
BI-6	23	275	190		
BI-5	19	135	110		
BJ-1	34	169*	117		
BJ-2	32	141*	100		
BJ-3	31	200	179		
BJ-5	27	225	102		
BJ-5x	29	286	145		
BJ-6	25	133*	91		
BJ-6x	22	208	112		
BJ-8	23	151*	104		
BJ-9	21	188	102		
BJ-10	18	119*	75		
BJ-11	16	116*			
BK-1	34	433	268	373	1317
BK-1x	34	163	101	263	595
BK-2	32	210	162		
BK-2x	27	152	112		
BK-3	30	433	268	267	
BK-3x	32	175			
BK-4x	22	227	170	150	
BK-5	25	333	300	358	
BK-6	23	170	120		
BK-6x	21	204	125		
BK-7	22	337	262	350	1140
BK-8	20	205	110		
BK-9	19	188	101		

TABLE I—*Continued*

Individual	Age as of March 1947	Total Cholesterol	Cholesterol Esters	Phospholipids	Total Lipids
CA-3	21	140	79		
CB-4	29	193*	135		
CB-4x	23	175	127		
CB-2	27	215	188	225	
CB-3	26	210	112	217	
CB-3x	21	200	117	175	
CC-1	29	175	127		
CC-1x	25	155	117		
CC-2	26	165	135		
CC-3	24	169*	119		
CC-4	22	183	123		
CC-5	19	167	117		
CC-7	10	170	95		
CF-1	12	182	135		
CF-2	15	250	150		
CF-3	3	175	100		
CG-2	3	170	115		
CG-3	5	170	130		
CH-1	6	200	97		
CH-2	2	187	117		
CI-3	8	158	110		
CI-1	5	200	115		
CL-1	9	187	121		
CL-2	7	250	116		
DA-1	2	175	83		
DF-1	5	183	112		
DG-1	9	406	233	380	1239
DG-2	7	196	140		
DG-3	6	196	140		
DG-4	5	341	281	455	1412
DH-1	7	153	105		
DH-2	6	160	100		
DH-3	3	160	210		
DI-2	5	205	95		
DI-1	2	152	110		
DJ-1	3	142*	101		
DK-1	3	165	135		
EF-2	6	153	116		
EF-1	3	208	142		
FC-1	57	237	102		
FC-2	48	196	130		

\* Schoenheimer-Sperry Method.

\*\* Determined in 1928.<sup>21</sup>

† Age at death.

6. Total cholesterol and cholesterol esters were determined on all. Phospholipids and total lipids were determined on all of the individuals in whom the blood cholesterol was increased, and on many of the normals (table 1).

The Bloor<sup>6</sup> method for determining blood cholesterol was used in the initial survey because of the large number to be studied. The method was changed to the more accurate and time-consuming technic of Schoenheimer-Sperry<sup>7,8</sup> when certain detailed metabolic studies, which are still under way, were begun. The values determined by the latter method are designated by an asterisk. Phospholipids were extracted and precipitated by the

method of Boyd,<sup>9</sup> and phosphorus was determined by the method of Fiske and Subbarow.<sup>10</sup> Total lipids and neutral fat were determined by the method of Boyd.<sup>9</sup> The correlation of the blood cholesterol levels with the genetic pattern of transmission revealed a clear-cut distinction between normal levels and abnormal elevation of the blood cholesterol (figure 1). We consider 280 milligrams per cent by the Bloor method and 210 by the Schoenheimer-Sperry method abnormal elevation. Only three of our normals (B-5, BC-1 and BJ-6) exceeded 260 milligrams per cent by the Bloor or 200 by the Schoenheimer-Sperry method.

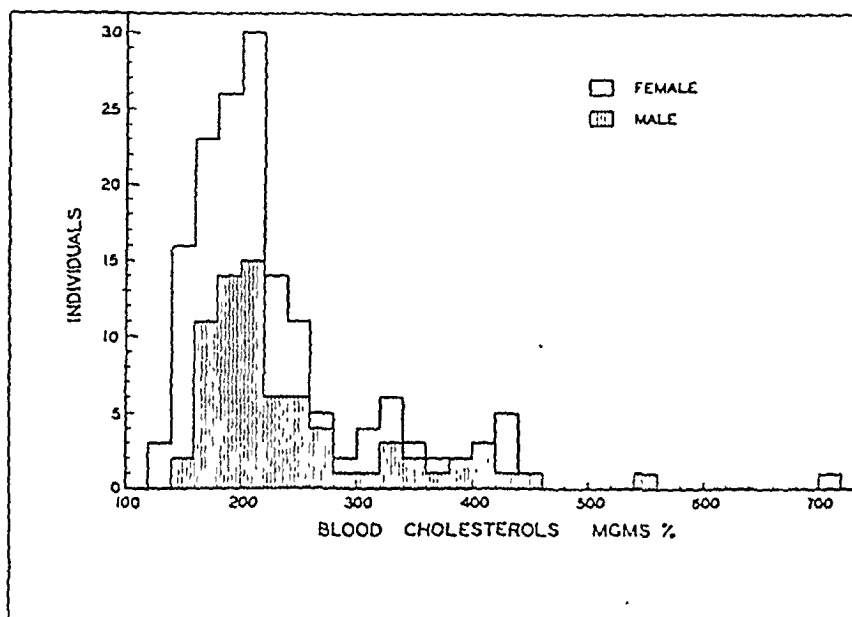


FIG. 1. Histogram of total blood cholesterol, plotted as Bloor values.

Many authors<sup>11, 12, 13, 14, 15, 16, 17, 18, 19, 20</sup> have pointed out that the condition under discussion is hereditary and several modes of transmission have been postulated. Svendsen<sup>15</sup> believes that increased cholesterol is a dominant trait. Müller<sup>13</sup> states that either xanthoma or increased cholesterol is a dominant, while Thannhauser and Schmidt<sup>19</sup> consider both recessive.

It is not difficult to understand these discrepancies when one realizes that it is rare to find reports in which two generations have been studied. Most of the reported families are small, or only a small number of the members was investigated. We have been able to study four generations of large families and to examine nearly all living members of most sibships.

It can be seen from the family tree (figure 2) that whenever one parent had an elevated blood cholesterol, approximately one-half of the children had an elevated blood cholesterol. This is shown to good advantage in sibships K and BK (figure 3).

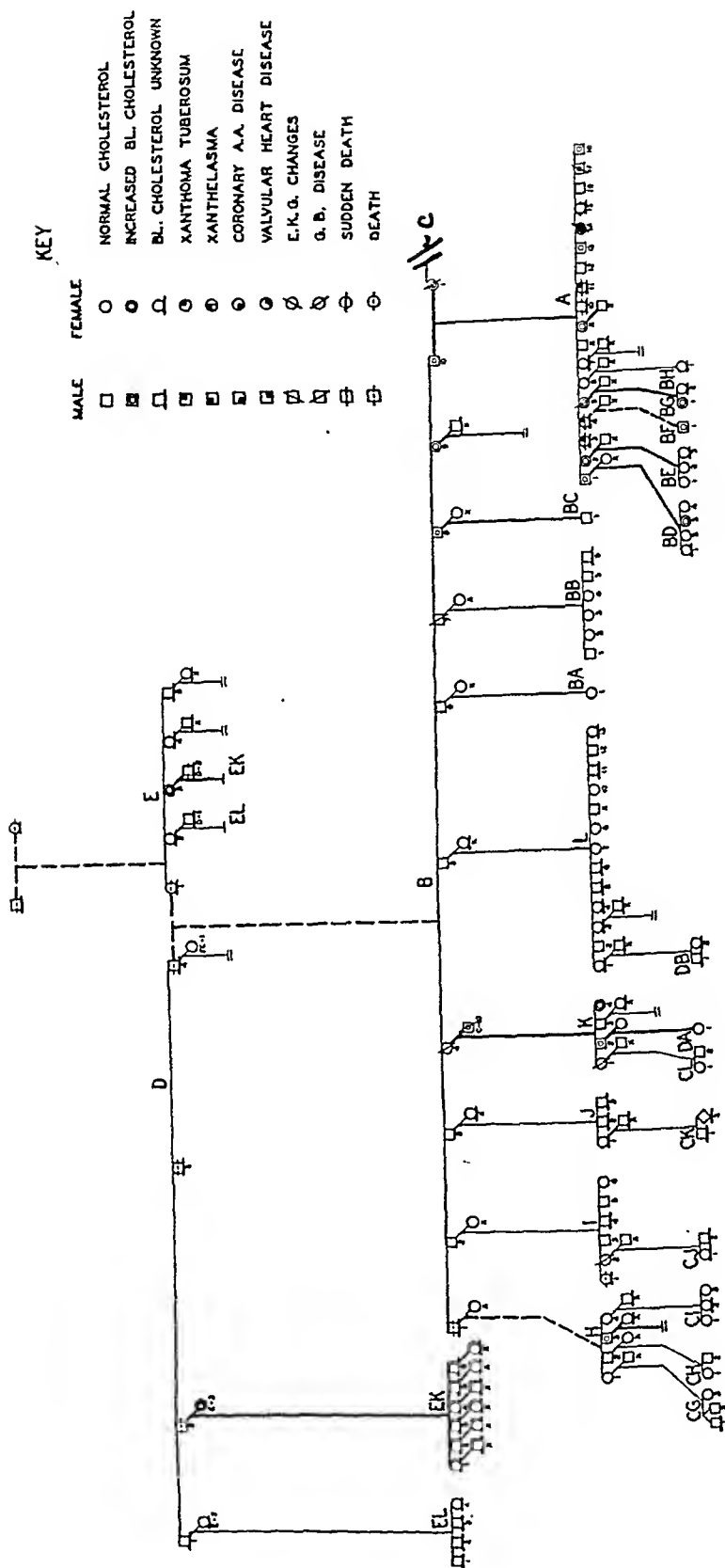


FIG. 2A.

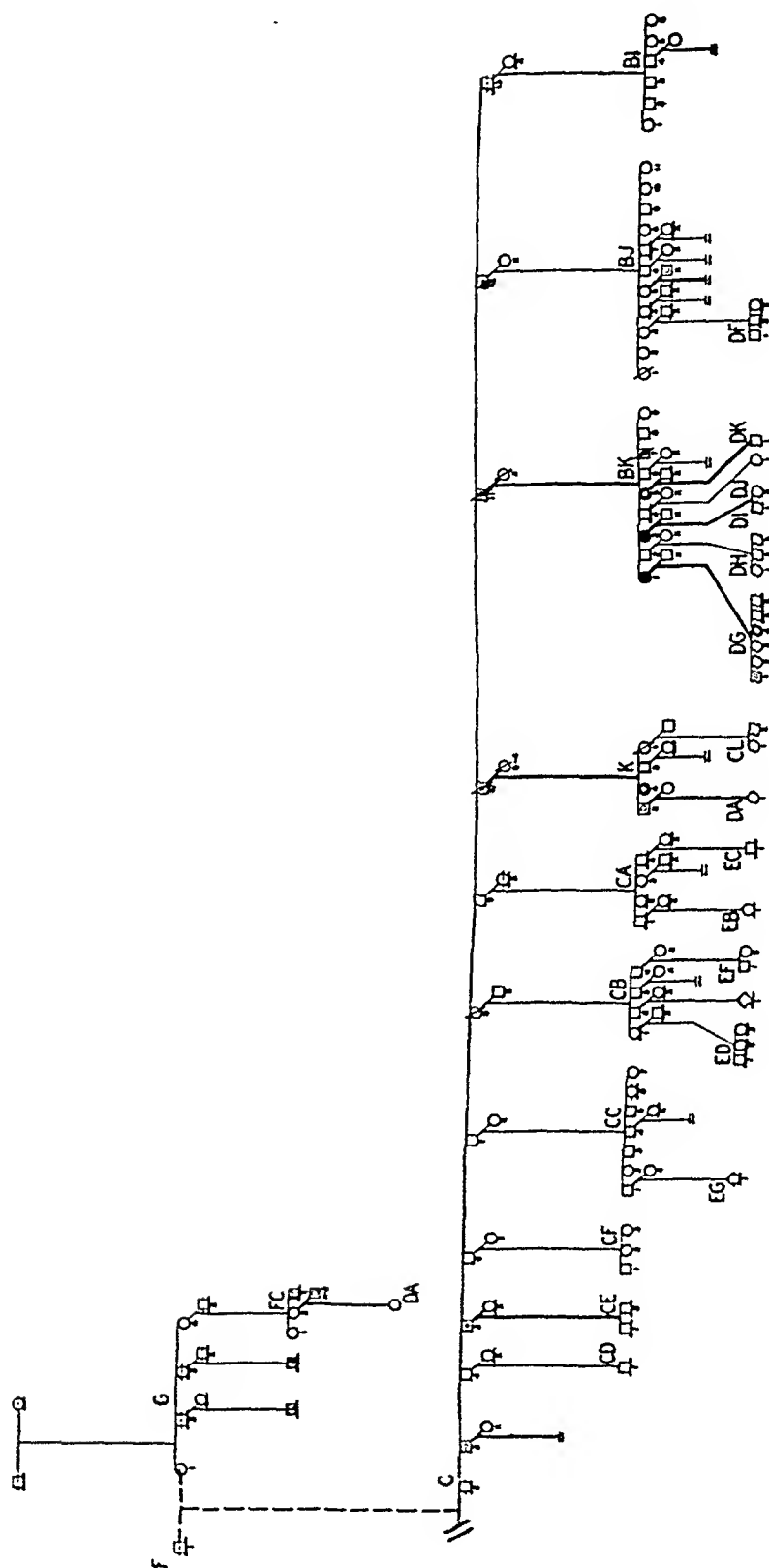


FIG. 2B.

Fig. 2A and 2B should be one continuous pedigree, but due to the large number of individuals involved, it has been necessary to split this into two figures. The two parallel lines at the end of Sibship B and Sibship C represent the point where the pedigree was broken. The heavy lines show the transmission of essential familial hypercholesterolemia. The heavy broken lines show presumptive transmission of this trait (i.e.) either both parents were unknown or one was normal and the other was unknown.

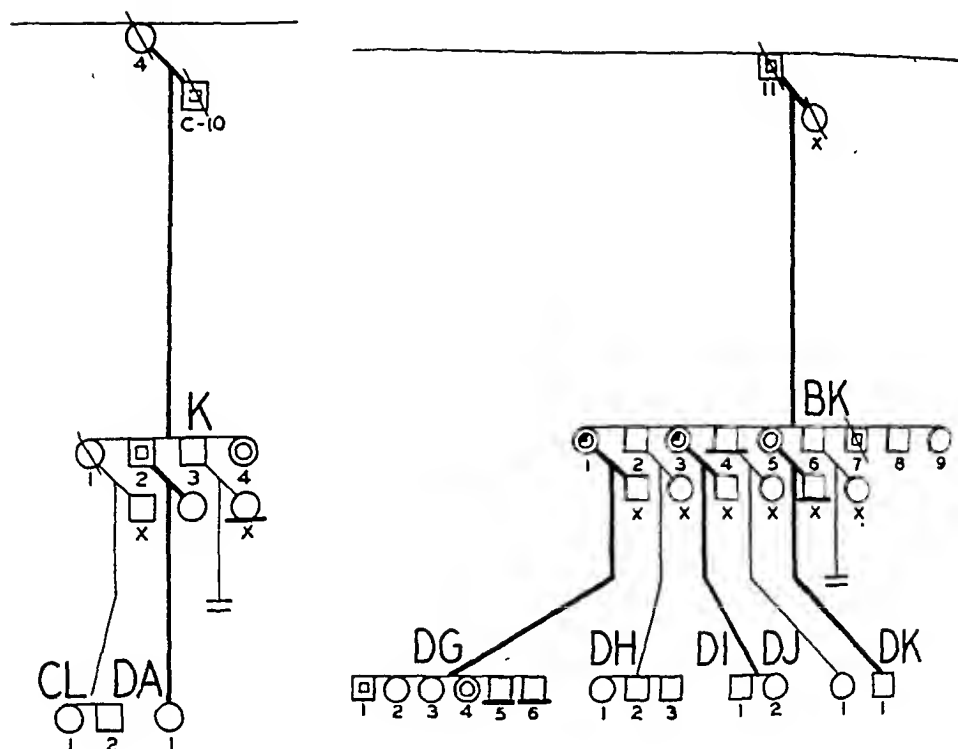


FIG. 3. Matings of heterozygous abnormal  $\times$  homozygous normal.

When neither parent had an increased blood cholesterol, all of the children studied showed normal blood levels. (See sibships BB, BJ and CC, figure 4.)

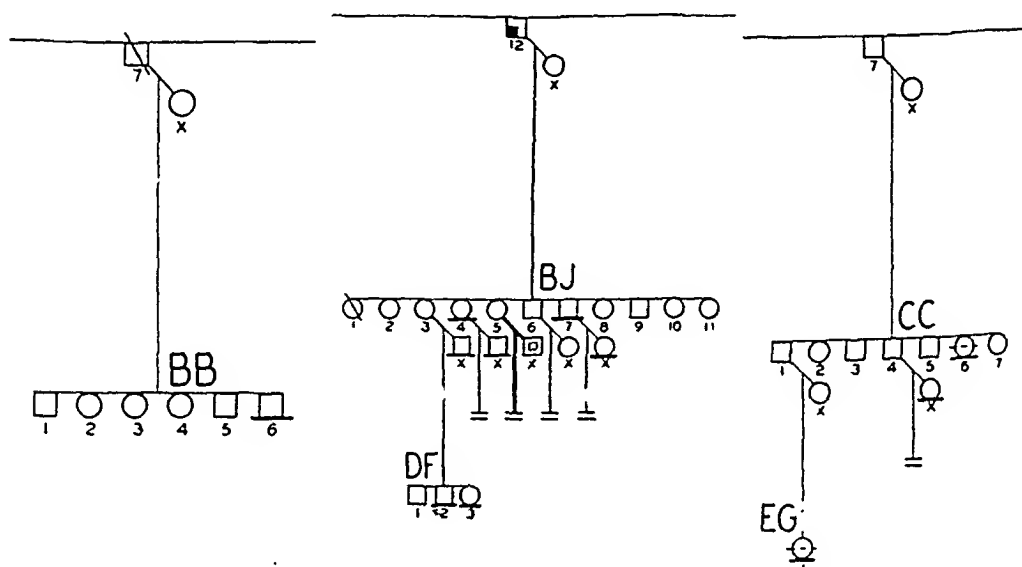


FIG. 4. Matings of homozygous normal  $\times$  homozygous normal.

In the marriage of C-1 and B-10, both had an increased blood cholesterol. Of their 18 children (sibship A, figure 5), five had xanthoma tuberosum and/or tendinosum. Six had elevated blood cholesterol *without*



skin lesions and four had normal blood cholesterol. Three are reported not to have had skin lesions, but their blood cholesterol level is not known.

In the union of A-4 (who had xanthoma tuberosum) and A-4x (whose blood cholesterol was normal) the only child (BF-1) showed an increased blood cholesterol (figure 5).

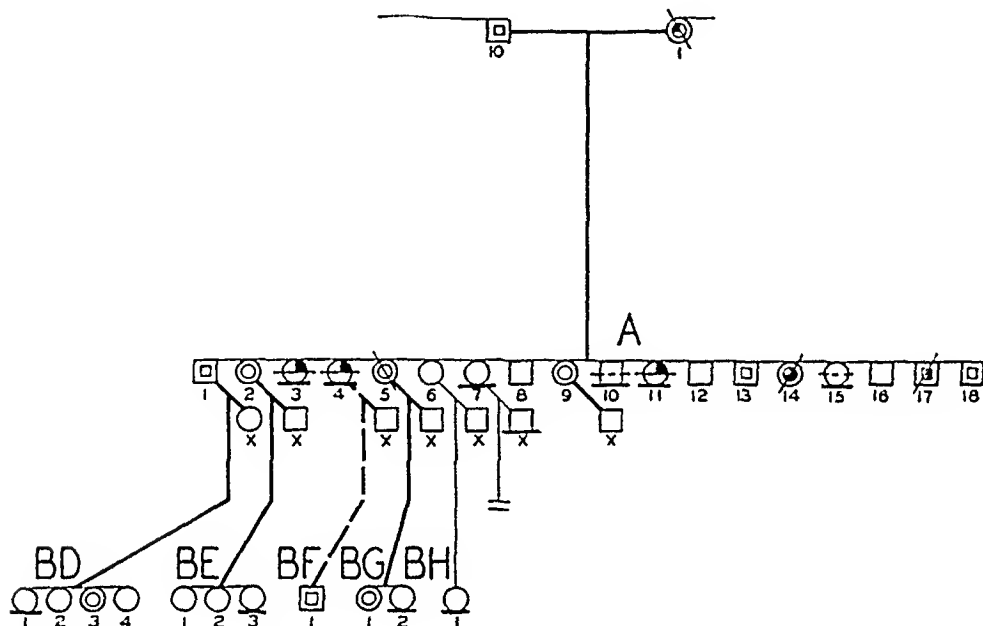


FIG. 5. Mating of heterozygous abnormal  $\times$  heterozygous abnormal, and xanthoma tuberosum (presumed homozygous abnormal)  $\times$  homozygous normal.

Of the five in sibship A who had xanthoma tuberosum and/or tendinosum (figure 6), only two (A-14 and A-17) were studied by us; but Curtis, Wile, Eckstein and Duemling<sup>21, 22, 23</sup> reported observation on two others (A-3 and A-4), and though blood cholesterol levels were not reported, these cases were typical clinically and pathologically. The family physician and parents report that A-11 was likewise typical.

It should be pointed out that there are two possible matings (homozygous abnormal  $\times$  homozygous abnormal and homozygous abnormal  $\times$  heterozygous abnormal) that we did not observe in this kindred. We feel, however, that our data are sufficiently complete and consistent to permit us to present a new theory concerning the mode of transmission (figure 7).

We postulate:

1. That the metabolic disorder characterized by increased blood cholesterol which is designated by "C" (as against a normal blood cholesterol designated as "c") is transmitted as a dominant.

2. Xanthoma tuberosum or tendinosum represents the homozygous abnormal.

3. A normal blood cholesterol represents the homozygous normal.

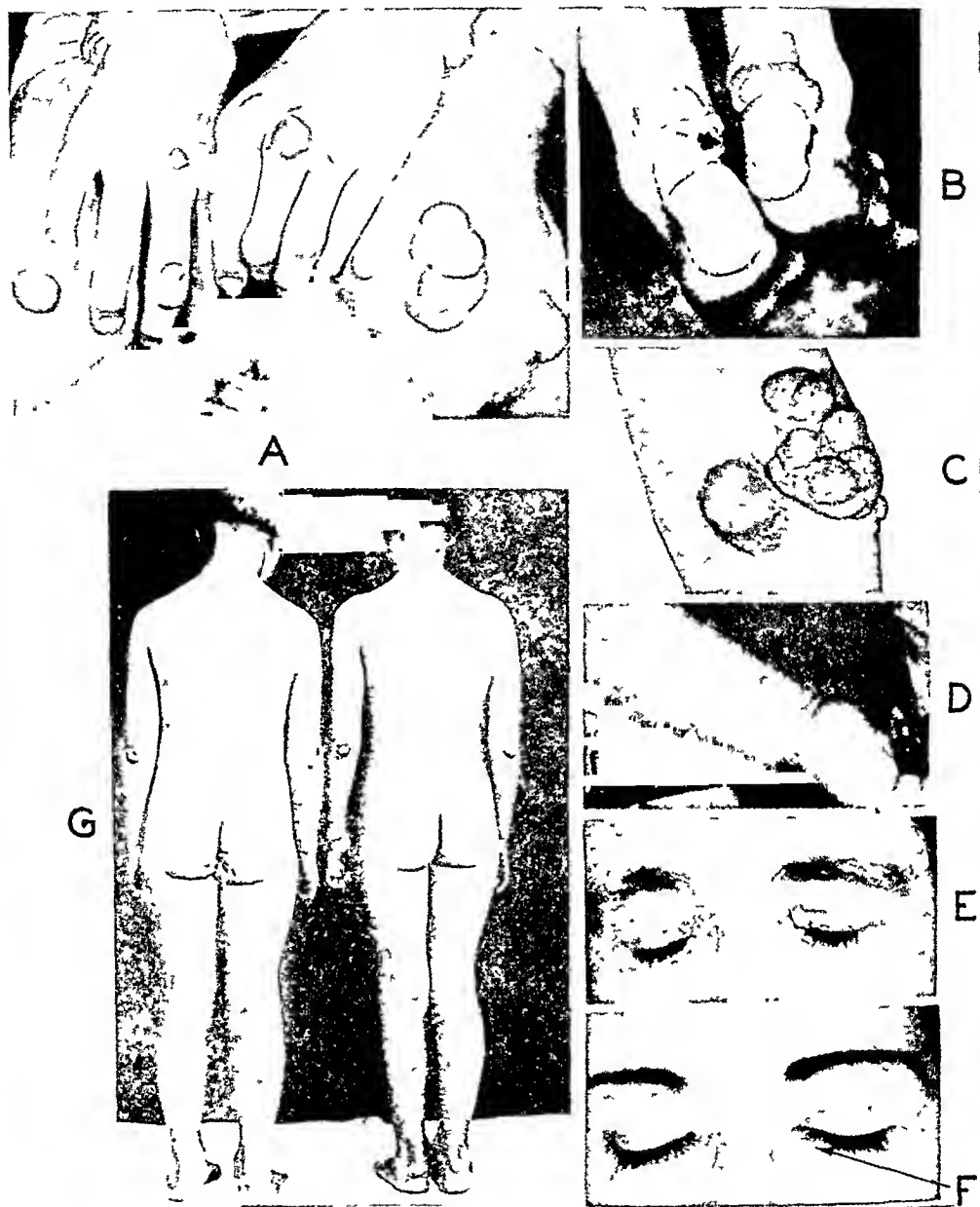


FIG. 6. A and C—Xanthoma tuberosum of A-14; B—Xanthoma tendinosum of A-14; D—Early xanthoma of A-17; E and F—Xanthelasmata of BK-1 and BK-3; G—Xanthoma tuberosum and tendinosum of A-3 and A-4.

This type of inheritance is known as "incomplete" <sup>24</sup> dominance because the severity of the condition is less in the heterozygote than in the homozygote.

A more detailed analysis of all the genetic data obtained will be presented by us at a later date and will include blood types and a number of test factors.<sup>25</sup>

The age incidence of the two groups is shown in figure 8.

It has been pointed out by many investigators <sup>4, 11, 16, 17, 19, 20, 27, 28, 29</sup> that certain clinical and/or anatomical abnormalities seem to be associated with xanthomatous deposits in the skin.

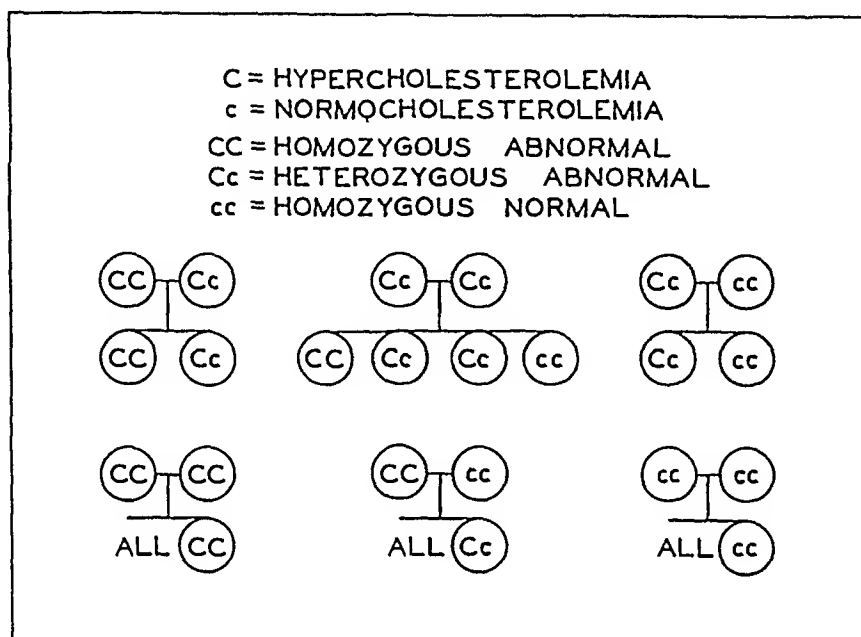


FIG. 7. Possible matings and predicted distribution of offspring.

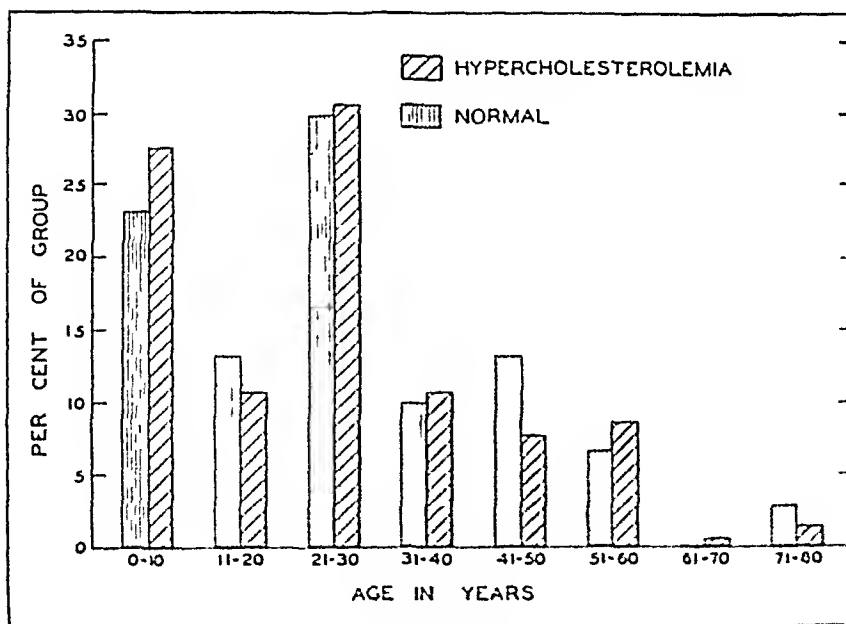


FIG. 8. Age incidence.

The relative frequency of these complications in essential familial hypercholesterolemia is shown in table 2.

It will be noticed that xanthoma tuberosum and/or tendinosum occurred in two of the hypercholesterolemic group, and they have been discussed.

Xanthelasma was present in three cases (C-1, BK-1 and BK-3) of the group with increased cholesterol, and in one case (G-1) in the group with normal blood cholesterol.

TABLE II  
Relative Frequency of Clinical and/or Anatomical Abnormalities

	Hypercholesterolemia (30)	Normocholesterolemia (129)	Statistical Significance $\chi^2$
Xanthoma {Tuberosum Tendinosum	(2) 6.6%	(0) —	—
Xanthelasma	(3) 10 %	(1) 0.8%	—
Arcus Juvenalis/Senilis	(0) —	(1) 0.8%	—
Angina Pectoris	(1) 3.3%	(1) 0.8%	—
Xanthomatous Valvular Heart Disease	(2) 6.6%	(0) —	—
Gall-Bladder Disease			
Clinical Story	(5) 17 %	(7) 5.4%	0.09
X-Ray Taken	(5)	(4)	—
X-Ray Positive	(2) 6.6%	(1) 0.8%	—
Heptomegaly	(5) 17 %	(3) 2.3%	0.01

Arcus senilis to our surprise was present in only one case (G-1) and here the cholesterol was normal. It should be pointed out, however, that a slit lamp was not used, as most of the examinations were done in the home.

Coronary artery disease as manifested by electrocardiographic changes and angina pectoris was found in one case of the hypercholesterolemic group (A-14). It should be emphasized that she was 11 years of age and had had symptoms for two years. There was one questionable case of angina in the group with normal cholesterol (C-12), his age being 59.

No diagnosis of myocardial infarction was made by us, but three (A-3, A-4 and A-11) died a sudden death before this study was begun; and as they had xanthoma tuberosum, infarction secondary to coronary atherosclerosis must be suspected.<sup>13, 14, 16, 18, 26, 27, 35</sup>

Valvular heart disease was present in A-14 and A-17. There was no history of rheumatic fever, scarlet fever, or chorea in either of these children. In view of the fact that Montgomery,<sup>4</sup> Müller,<sup>13, 14</sup> and Cook et al.<sup>35</sup> have reported xanthomatous deposits on the valves of the heart, we feel justified in assuming that the valvular defects are due to them.

A detailed analysis of the electrocardiographic findings and cardiac status of this kindred will be presented elsewhere.<sup>30</sup>

We did not see any cases of biliary cirrhosis. Enlargement of the liver, however, was present in five cases (A-14, C-5, K-2, BK-7 and DG-1) of those with hypercholesterolemia and in three cases (K-1, BJ-2, and CB-2) of those with normal blood cholesterol. None of the eight gave a history of jaundice or had increased urobilinogen in the urine; hepatomegaly was unexplained.

A clinical story suggestive of gall-bladder disease was given in five instances (A-5, C-1, C-10, BK-7 and C-11) in the hypercholesterolemic group: cholecystograms, however, were positive in only two (A-5 and C-1). A similar story was obtained seven times in the normal group (B-4, B-7, C-8, I-2, K-1, BJ-1 and C-11). Except for three (B-7, C-8, and BJ-1), these were also x-rayed but only one (B-4) had a positive cholecystogram.

Hypertension was found in two cases with increased cholesterol (BK-7 and E-3) and in one case of normal cholesterol (B-4).

Splenomegaly was not found in this kindred.

The occurrence of secondary xanthoma in uncontrolled diabetes has long been known. It has been suggested by several authors<sup>1, 21, 22, 23, 31</sup> that there is some relation between primary xanthoma and diabetes, or at least a

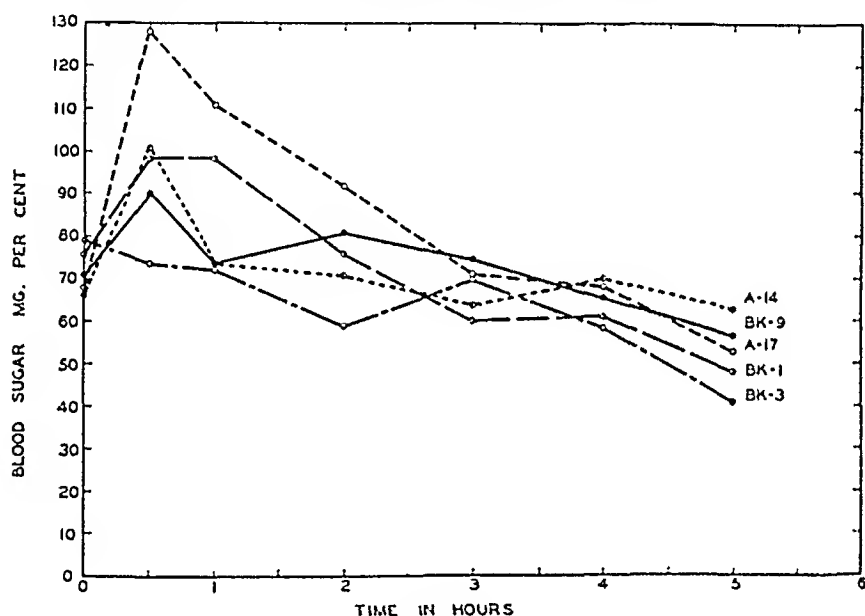


FIG. 9. Five hour glucose tolerance tests, showing normal utilization of carbohydrate.

decreased carbohydrate tolerance. Wile, Curtis, and Eckstein<sup>21, 22</sup> published so-called prediabetic glucose tolerance tests on two members of this kindred (A-3 and A-4). It must be pointed out, however, that these patients had been on a diet restricted both in carbohydrate and calories. In 1890 Hoffmeister<sup>30</sup> showed that a diabetic-like curve could be produced by starvation. Himsworth<sup>32</sup> has pointed out the necessity of properly preparing patients before doing a glucose tolerance test.

In view of the above, it was thought advisable to study the carbohydrate tolerance in this group.

Two patients with xanthoma tuberosum (A-14 and A-17) representing the homozygous abnormal; two patients with increased blood cholesterol and xanthelasma (BK-1 and BK-3) representing the heterozygous abnormal; and one patient (BK-9) with normal blood cholesterol representing the

homozygous normal were placed on the standard University of Michigan glucose tolerance test preparatory diet (300 grams carbohydrate, 80 grams protein and 2800 calories) for three days, and then five hour glucose tolerance tests were performed (the dose of glucose being 1.75 grams per kilo of ideal weight). All of the five glucose tolerance tests (figure 9) were normal. There is, then, no reason to expect people with essential familial hypercholesterolemia to show an altered tolerance to carbohydrate if they have been properly prepared for the test. Individuals with xanthoma tuberosum, therefore, do not belong in the group of potential diabetics.

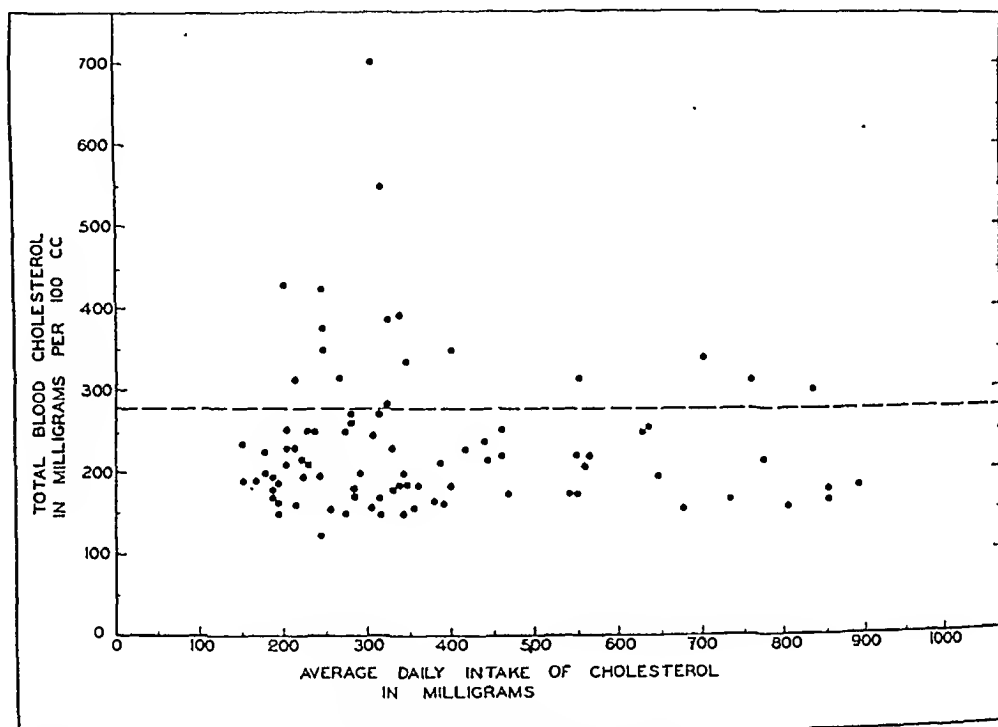


FIG. 10. The broken line designates hypercholesterolemia. Total blood cholesterol plotted as Bloor values.

As was mentioned above, an attempt was made to correlate the dietary cholesterol intake with the blood cholesterol. Figure 10 shows no association between the amount of cholesterol ingested and the blood cholesterol in either the normal or abnormal groups.

#### SUMMARY AND CONCLUSIONS

1. The metabolic disorder characterized by increased blood cholesterol is best described by the term essential familial hypercholesterolemia.
2. This condition is inherited as an "incomplete" dominant.
3. Xanthoma tuberosum represents the homozygous abnormal in this condition.
4. The upper limit of normal for blood cholesterol has been established by the genetic pattern of transmission.

5. The relatively greater incidences of certain pathological states in this condition, as compared with normal individuals is pointed out.

6. We were unable to demonstrate any delay in the utilization of carbohydrate in this condition.

7. The increase in blood cholesterol is endogenous, not dietary.

The authors are gratefully indebted to Dr. Fred H. Drummond of Kawkawlin, Michigan, who has observed this family for a number of years and, though too busy in the private practice of medicine to enter into this investigation, saw the value of such a study and was a constant source of information and encouragement.

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# SUBJECTIVE MANIFESTATIONS OF THE HYPER-ACTIVE CAROTID SINUS REFLEX \*

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It has been known for hundreds of years that pressure applied to the carotid sinus region may result in unconsciousness and convulsions. According to Ask-Upmark,<sup>1</sup> the Assyrians used this method to dull pain during the rites of circumcision. Perry<sup>2</sup> observed this phenomenon in 1779. The mechanism of its production, however, was not clearly understood until the pioneer work of Hering<sup>3</sup> and of Heymans.<sup>4</sup> These authors demonstrated that stimulation of the carotid sinus region results in a number of reflexes, the most prominent of which are those of cardioinhibition, vasodepression, and disturbances in respiration. This was followed by the work of other authors, notably that of Weiss and Baker,<sup>5</sup> Ferris and co-workers,<sup>6</sup> and Weiss and co-workers,<sup>7</sup> who demonstrated that unconsciousness and convulsions induced by the carotid sinus reflex were due in different individuals to stoppage of the heart or to a marked drop in blood pressure or to a direct cerebral effect.

In previous communications<sup>8,9</sup> I showed in large groups of cases that the cardioinhibitory and vasodepressor reflexes occur most frequently and in greater degrees in older age groups, in males, and in arteriosclerotic heart disease.

This paper deals with the various subjective manifestations that may be elicited by the carotid sinus reflex and their relative frequency of occurrence.

## MATERIAL AND METHODS OF STUDY

The series consisted of 1,193 cases, made up of 750 males and 443 females. Their ages ranged between 15 and 75 years, the majority being over 35 years. Most of the cases were ambulatory office patients who had a greater or less degree of cardiovascular disease, mainly arteriosclerotic. Many had had one or more episodes of coronary occlusion in the past. There were also cases who suffered from other constitutional disturbances or from various forms of neuroses.

The test was performed in most cases in the sitting position, except in those who were bedridden. It was observed, as by Weiss and co-workers before, that in the sitting position the response was quicker and more pronounced. The head was extended backwards, and the carotid arteries at the level of the cricoid cartilage were located and were gradually compressed against the spinous processes. It is essential that pressure be exerted slowly and with progressively greater force, for in extremely hypersensitive persons comparatively little pressure may bring about alarming symptoms.

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TABLE I

Symptom Complexes Exhibited by Carotid Sinus Stimulation in Order of Frequency

Description of Symptom Complexes	No. of Cases	Per Cent of Those Responding	Per Cent of Entire Series Tested
Dizziness	62	6.4	5.2
Dizziness and inequality of pupils	49	5.1	4.2
Unconsciousness	40	4.1	3.4
Dizziness and flushing	32	3.3	2.7
Unconsciousness and convulsions	28	2.9	2.3
Unconsciousness and inequality of pupils	25	2.6	2.1
Dizziness and pallor, followed by flush, ipsilateral pupil dilated	24	2.5	2.0
Dizziness and cough	24	2.5	2.0
Confusion, dazed, and amnesia	23	2.4	1.9
Pallor	21	2.2	1.8
Dizziness and fainting sensation	20	2.1	1.7
Dizziness and weakness	19	2.0	1.6
Ipsilateral pupil larger	17	1.8	1.5
Dizziness and choking	16	1.7	1.4
Dizziness and fullness in head	16	1.7	1.4
Dizziness, pallor, fainting, and weakness	16	1.7	1.4
Unconsciousness, convulsions, flushing, pallor, and dizziness	16	1.7	1.4
Pallor followed by flush, darkness in eyes	16	1.7	1.4
Warmth in head	16	1.7	1.4
Dizziness and perspiration	15	1.5	1.3
Dizziness and darkness in eyes	15	1.5	1.3
Dizziness, marked weakness, fainting, and darkness in eyes	14	1.4	1.2
Electric shock, pupils dilated	14	1.4	1.2
Dizziness and warmth in head	13	1.3	1.1
Unconsciousness, dizziness, and pallor	13	1.3	1.1
Cough, pallor and flush	13	1.3	1.1
Blurred vision and general body warmth	13	1.3	1.1
Dizziness, cough, darkness of eyes, and slight warmth	12	1.2	1.0
Dizziness, cough, and darkness of eyes	11	1.1	0.92
Dizziness, flushing, nausea, spots before eyes, and clonic movements of extremities	11	1.1	0.92
Unconsciousness, sweating, dizziness, and dilated ipsilateral pupil	11	1.1	0.92
Dyspnea, warmth in head, headache	11	1.1	0.92
Fatigue	11	1.1	0.92
Dizziness and clonic contractions of local groups of muscles	10	1.0	0.84
Dyspnea and pallor	10	1.0	0.84
Tremors and weakness	9	0.9	0.75
Dizziness, flushing, darkness in eyes, fullness in head, and warmth in entire body	9	0.9	0.75
Unconsciousness, blurred vision, flush followed by pallor and ipsilateral pupil dilated	9	0.9	0.75
Unconsciousness, darkness in eyes, and tingling	9	0.9	0.75
Dyspnea, choking, heat in ipsilateral ear, and pallor	9	0.9	0.75
Warmth of body	9	0.9	0.75
Pallor, followed by flushing	9	0.9	0.75
Crying spell	8	0.8	0.67
Dizziness, weakness, and dyspnea	8	0.8	0.67
Dizziness, sensation of heat, stifling of breath, unsteadiness, and muscular incoördination	8	0.8	0.67
Dizziness and ipsilateral pupil dilated	8	0.8	0.67
Palpitation (premature contractions)	8	0.8	0.67
Dizziness, choking sensation, and dilated pupils	7	0.7	0.59
Dizziness, fainting sensation, numbness of lips, and inequality of pupils	7	0.7	0.59

TABLE I—Continued

Description of Symptom Complexes	No. of Cases	Per Cent of Those Responding	Per Cent of Entire Series Tested
Dizziness, darkness and pain in right eye, and blurred vision	7	0.7	0.59
Dizziness, sense of light in left eye, and pallor	7	0.7	0.59
Unconsciousness, convulsions, darkness, tingling, dizziness, weakness, palpitation, and dyspnea	7	0.7	0.59
Fainting and flashes before eyes	7	0.7	0.59
Flushing	7	0.7	0.59
Flushing and ipsilateral pupil dilated	7	0.7	0.59
Weakness and ipsilateral pupil dilated	7	0.7	0.59
Choking sensation	6	0.6	0.50
Nausea	6	0.6	0.50
Dizziness, nausea, confusion, general warmth, and ipsilateral pupil dilated	5	0.5	0.42
Dyspnea, cough, and faintness	5	0.5	0.42
Dyspnea and pain in head	5	0.5	0.42
Choking sensation and sense of heat in ipsilateral ear	5	0.5	0.42
Inequality of pupils	5	0.5	0.42
Pins and needles, numbness, and pupils larger	5	0.5	0.42
Dizziness, nausea, and palpitation	4	0.4	0.34
Dizziness and crying spells	4	0.4	0.34
Dizziness, noises in head, and blurred vision	4	0.4	0.34
Unconsciousness, crying spell, dyspnea, and flushing of face	4	0.4	0.34
Unconsciousness and dyspnea	4	0.4	0.34
Headache	4	0.4	0.34
Right pupil larger	4	0.4	0.34
Darkness in eyes	4	0.4	0.34
Dizziness and nausea and perspiration	3	0.3	0.25
Dizziness and lacrimation	3	0.3	0.25
Dizziness, weakness, and blurred vision	3	0.3	0.25
Unconsciousness and numbness	3	0.3	0.25
Tightness in throat and chest	3	0.3	0.25
Dyspnea, confusion, and weakness	3	0.3	0.25
Dyspnea and cough	3	0.3	0.25
Dyspnea, fatigue, and warmth in face	3	0.3	0.25
Blurred vision	3	0.3	0.25
Fatigue and belching	3	0.3	0.25
Pain in left ear	3	0.3	0.25
Tightness in chest and throat	3	0.3	0.25
Dizziness and warmth on side stimulated	2	0.2	0.17
Dizziness and vibrations in neck	2	0.2	0.17
Dyspnea, cough, and sense of bulging of eyes	2	0.2	0.17
Dizziness, pallor, and perspiration	2	0.2	0.17
Weakness in right face	2	0.2	0.17
Pallor, followed by flush and epigastric distress	2	0.2	0.17
Dizziness, crying spell, and dryness of tongue	1	0.1	0.08
Dizziness, weakness, dryness in mouth, pallor, and flush	1	0.1	0.08
Dizziness, and dead feeling in left hand	1	0.1	0.08
Dizziness, fear of falling, dyspnea, and ipsilateral pupil dilated	1	0.1	0.08
Choking, cough, pallor, and sense of swelling of tongue	1	0.1	0.08
Blurred vision, and pain of ipsilateral ear	1	0.1	0.08
Bitter taste, numbness	1	0.1	0.08
Stiffness of neck	1	0.1	0.08
Weakness, tingling of left hand, ipsilateral pupil dilated, cough	1	0.1	0.08
Pressure in head, ipsilateral pupil dilated	1	0.1	0.08
Tingling sensation hands	1	0.1	0.08

For the same reason, the test should be performed on one side of the neck at a time.

In cases where marked slowing or stoppage of the heart occurred, the pressure was continued until other symptoms developed. The same was true with the vasodepressor reflex. In cases where no cardioinhibition or vasodepression occurred, the carotid sinus compression was continued until all possible subjective disturbances could be elicited or until it was demonstrated that the individual was not to be affected. Usually, compression of one or the other carotid sinus for 15 seconds was sufficient to bring about all manifestations in the given individual, although some responded in four seconds and others required about a minute to exhibit the various manifestations.

TABLE II

Degrees of Cardioinhibition in Their Relation to the Frequency of Subjective Manifestations of the Carotid Sinus Reflex

Degrees of Cardioinhibition	Cases Showing Subjective Manifestations		Cases Showing No Subjective Manifestations	
	No. of Cases	Per Cent	No. of Cases	Per Cent
0	153	15.8	49	22.0
+	160	16.5	41	18.4
++	214	22.1	49	22.0
+++	198	20.4	46	20.6
++++	245	25.3	38	17.0

0, no cardioinhibition; +, less than 10 per cent slowing of the heart; ++, 10 to 30 per cent slowing of the heart; +++, 30 to 70 per cent slowing of the heart; +++, stoppage of the heart for three seconds or more.

TABLE III

Incidence of Change in Blood Pressure in Relation to the Frequency of Subjective Manifestations of the Carotid Sinus Reflex

Blood Pressure	Cases Showing Subjective Manifestations		Cases Showing No Subjective Manifestations	
	No. of Cases	Per Cent	No. of Cases	Per Cent
Drop	674	69.5	132	59.2
No drop	257	26.5	75	33.6
Rise	39	4.0	16	7.2

To determine whether any relationship exists between the various subjective manifestations and the degrees of cardioinhibition, if present, the cases were divided into various grades of cardiac slowing, as follows: 0, indicating no slowing; 1 +, slowing less than 10 per cent; 2 +, slowing 10 per cent to 30 per cent; 3 +, slowing 30 per cent to 70 per cent; and 4 +, where the heart stopped for at least three seconds. To determine whether there is any relationship between the various subjective manifestations to vasodepression, the cases were divided into those that did and those that

did not show the various manifestations and each group was subdivided into those that did and those that did not show a drop in blood pressure.

### OBSERVATIONS

Of the 1193 cases tested, 970, or 81.3 per cent, showed one or more subjective disturbances and often, also, abnormal objective findings in addition

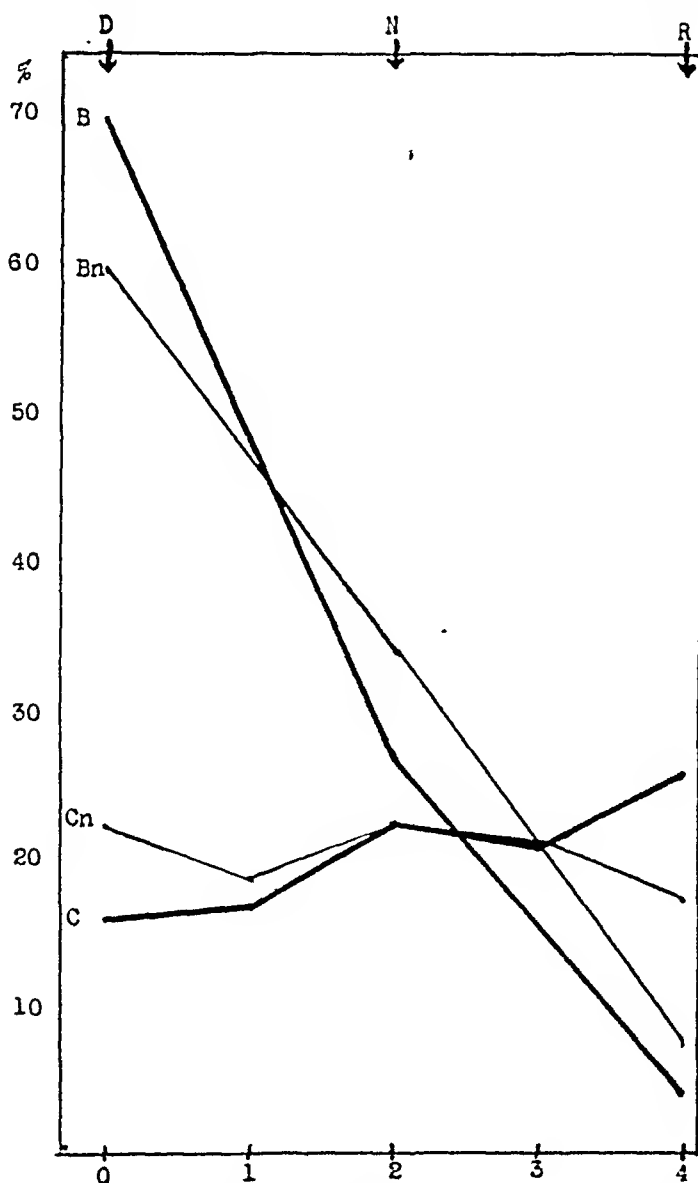


FIG. 1. Percentual relationship of cardioinhibition, blood pressure changes and subjective manifestations. B and Bn, blood pressure curves in cases with and without subjective manifestations respectively. D cases with drop in pressure, N cases with no drop in pressure, and R cases with rise in pressure.

C and Cn, cardioinhibition curves in cases with and without subjective manifestations, respectively. 0, no cardioinhibition; 1, slowing less than 10 per cent; 2, slowing 10 to 20 per cent; 3, slowing 30 to 70 per cent; 4, stoppage of the heart for at least 3 seconds.

to cardioinhibition and vasodepression. In some cases there was only one complaint on the part of the patient, and in others two or more complaints or objective findings. The various manifestations were of diverse character and occurred singly or in various combinations in different individuals. Comparatively few cases exhibited exactly similar manifestations. All the symptoms were definitely more marked and more diverse in the older age groups.

In some, the abnormalities occurred upon pressure of the carotid sinus on one side and not on the other. In others, the same abnormalities developed upon pressure on either one or the other side in the same case, but to different degrees. In still others, some symptoms developed when pressing one side and other symptoms when pressing the other.

TABLE IV

Analysis of Individual Symptoms in Order of Frequency, Grouped under Disturbances of the Effector Structures of Organs

Organic Disturbances and Their Manifestations	No. of Cases	Per Cent of Those Responding	Per Cent of Entire Series Tested
I. Cerebral disturbances	822	84.7	68.8
Dizziness and related sensations	508	52.4	42.5
Unconsciousness	169	17.4	14.2
Fainting sensation	69	7.1	5.8
Confusion, dazed and amnesia	54	5.7	4.5
Crying spells	17	1.8	1.4
Noises in head	4	0.4	0.3
Fear of falling	1	0.1	0.1
II. Eye disturbances	394	40.6	33.0
Pupils unequal (ipsilateral dilated)	206	21.2	17.3
Darkness in eyes	85	8.8	7.1
Blurred vision, shine in eye	47	4.8	3.9
Both pupils dilated	26	2.7	2.2
Spots before eyes	11	1.1	0.9
Pain in eye	7	0.7	0.6
Lacrimation	3	0.3	0.3
Sense of bulging of eyes	2	0.2	0.2
III. Vasomotor disturbances	283	29.2	23.7
Pallor	108	11.1	9.1
Flushing	92	9.5	7.7
Pallor followed by flushing	43	4.4	3.6
Sweating	31	3.2	2.6
Flush followed by pallor	9	0.9	0.8
IV. Sensory disturbances	214	22.1	17.9
Sense of warmth, general, head ipsilateral side of face or ear	106	10.9	8.9
Pressure and fullness in head	32	3.3	2.7
Tingling and electric shock	25	2.6	2.1
Headache and pain in head	20	2.1	1.7
No change in head	19	2.0	1.6
Pins and needles	5	0.5	0.4
Pain in ipsilateral ear	3	0.3	0.3
Vibrations of neck	2	0.2	0.2
Dead feeling in hands	1	0.1	0.1
Stiffness of neck	1	0.1	0.1

TABLE IV—Continued

Organic Disturbances and Their Manifestations	No. of Cases	Per Cent of Those Responding	Per Cent of Entire Series Treated
V. Respiratory disturbances	171	17.6	11.3
Dyspnea	80	8.2	6.7
Cough	60	6.2	5.0
Choking sensation	23	2.4	1.9
Stifling of breath	8	0.8	0.7
VI. Somatic muscular disturbances	102	10.5	8.6
Generalized convulsions	74	7.6	6.2
Local tremors and clonic movements	20	2.1	1.7
Unsteadiness	8	0.8	0.7
VII. Constitutional disturbances (weakness-fatigue)	96	9.9	8.0
VIII. Gastrointestinal disturbances	38	3.9	3.2
Nausea	29	3.0	2.4
Belching	3	0.3	0.3
Epigastric distress	2	0.2	0.2
Dryness of tongue and mouth	2	0.2	0.2
Bitter taste	1	0.1	0.1
Sensation of swelling of tongue	1	0.1	0.1
IX. Cardiac abnormalities (aside from slowing or stoppage)	22	2.4	1.8
Palpitation due to premature contractions	19	2.0	1.6
Pain, tightness in chest and throat	3	0.3	0.3

The various symptom-complexes are shown in order of frequency in table 1. It will be observed that the most common are those of dizziness, alone or in combination with other disturbances, followed in some cases by coma and convulsions. Some cases developed symptoms without marked slowing or stoppage of the heart or a drop in blood pressure. Alarming symptom-complexes, however, occurred most frequently among individuals who showed stoppage of the heart or a marked drop in pressure.

The numerical and percental relationships of the subjective manifestations to cardioinhibition and blood pressure changes are shown in tables 2 and 3 and in figure 1.

The various symptom-complexes observed were broken up into individual symptoms and classified in groups under the effector structure or organ. These are shown in table 4.

## DISCUSSION

It will be observed that in the great majority of patients who seek medical attention for various conditions, a hyperactive carotid sinus reflex will induce various subjective and objective disturbances besides cardioinhibition and vasodepression. In our series of 1,193 cases, most of whom had some form of cardiovascular disease, 970, or 81.3 per cent, showed such disturbances.

The disturbances varied in their character and intensity, and occurred in different combinations. The most frequent were dizziness alone or in

combination with other symptoms. More severe disturbances which occurred next in frequency were complete unconsciousness, with or without convulsions. Some experienced mere confusion, amnesia, crying spells, and so on. Next in succeeding order of frequency were disturbances referable to the eyes, the vasomotor system, the sensory organs, the respiratory system, the muscular system, the constitutional state, the gastrointestinal system, and the heart.

The diversity of disturbances induced by the reflex speaks for a widespread distribution in the central nervous system of the afferent nerve impulses originating in the carotid sinus area.

It is of interest to observe that unconsciousness and convulsions, with the associated manifestations due to the carotid sinus reflex, occurred in some of our cases who never had spontaneous attacks. It was also observed that some patients who gave a history of one or more attacks of spontaneous dizziness, fainting, or unconsciousness not due to demonstrable disease of the central nervous system did not present these symptoms on carotid sinus pressure. Evidently reflexes originating in other parts of the body may produce the same cerebral manifestations.

Of the milder grades of symptoms of carotid sinus origin, many cases gave histories of spontaneous disturbances of the same nature. Others never experienced such disturbances until the test was applied. Still others gave a history of disturbances of like nature which could not be reproduced by the reflex.

A proper knowledge of the mechanism of the production of the various manifestations of the hyperactive carotid sinus reflex is of considerable importance, as it might elucidate the nature of symptoms in various disease states. The work of Weiss, Capp, and Ferris has helped to clarify the mechanism of the unconscious states and convulsions induced by this reflex. They have demonstrated that this syndrome is caused by cerebral ischemia due to cardiac asystole, extreme drop in blood pressure or to a direct cerebral effect, probably cerebral angiospasm. In some cases only one factor may be operative; in others, two; in still others, all three.

Judging from our findings, the direct cerebral factor appeared to occur fairly frequently. In many cases fainting and unconsciousness, with or without convulsions, occurred without stoppage of the heart or a marked drop in pressure. In others, where the stoppage of the heart had occurred, unconsciousness developed after the heart had returned to a normal or even faster than normal rate. In these cases, therefore, the manifestations were evidently caused by a direct reflex effect on the brain, producing either cerebral vascular spasm or changes in the synapses of various neuron connections. It appears that the health of the blood vessels supplying the brain is an important factor in the production of the cerebral manifestation. Individuals who suffered from cerebral arteriosclerosis showed the most alarming cerebral symptoms.



The various forms of response to the carotid sinus reflex speak against the possibility that hypersensitivity of the carotid sinus itself is responsible for the reflex reactions, unless we postulate the theory that the carotid sinus receptor organs are end organs of nerve fibers leading to different areas of the central nervous system in different individuals. Such wide anatomical variation is hardly possible. It is more likely that the variability in the reactions is dependent upon the sensitivity of the synaptic connections in the central nervous system, and upon the sensitivity of the various effector nerves or their endings in the effector structures or organs in different individuals. The reflex may therefore be used as an index in some cases of the functional state of these various parts of the central neurons, the efferent arms of the arc, or of the effector organ.

If, as it appears, the hypersensitivity is in the central neurons or in the efferent arm of the arc, therapy directed to the carotid sinus region alone must have great limitations. In cases where unconsciousness and convulsions occur as a result of comparatively little carotid sinus stimulation, such as by bending the head or by the pressure of a tight collar, and where the syndrome can be easily reproduced by comparatively little pressure on the carotid sinus, good results may be expected from surgical extirpation of the nerve connections in the carotid sinus region. Although this procedure will not alter the inherent sensitivity of the central neuron connections or the efferent arms of the arc, it will remove the impulses arising from the carotid sinus region. This appears to be substantiated by the result of operation on 13 cases by Craig and Smith.<sup>10</sup> They obtained excellent results in four cases, good results in one, fair in four, and poor in the rest. In cases where no spontaneous attacks occur and disturbances arise only as a result of stimulation of the carotid sinus, or in cases where manifestations like those arising from the carotid sinus reflex occur and cannot be reproduced by carotid sinus pressure, operative interference is useless.

A word of caution must be given in performing the carotid sinus reflex test. Inasmuch as the most severe reactions occur in the presence of cerebral arteriosclerosis, great care must be exercised in performing the test in the presence of this condition. Marmor and Sapirstein<sup>11</sup> have reported a case of bilateral thrombosis of the anterior cerebral artery following carotid sinus stimulation. Askey<sup>12</sup> reported seven cases of contralateral hemiplegia following carotid sinus pressure. I have encountered several instances of transient palsies and speech disturbances following carotid sinus stimulation. In two cases, complete hemiplegia occurred. All these cases had marked evidence of cerebral arteriosclerosis.

#### SUMMARY

In 1,193 cases tested for hyperactivity of the carotid sinus reflex, 970, or 81.3 per cent, showed various subjective disturbances, besides cardioinhibition and vasodepression. In order of frequency, they consisted of dizziness,

unconsciousness and convulsions, abnormal sensation referable to the eyes, the vasomotor system, the sweat glands, the organs of sensation, the respiratory system, the somatic muscular system, the general constitutional state, the gastrointestinal system, and the heart. Individuals of the older age groups, especially those with cerebral arteriosclerosis, showed the greatest number and degrees of disturbances.

Many individuals who exhibited the various manifestations on carotid sinus pressure did not suffer from spontaneous attacks. Some individuals who experienced spontaneous attacks did not develop such attacks on carotid sinus pressure. In still others, carotid sinus pressure reproduced the symptom-complexes which the patient experienced spontaneously or as a result of bending the head or other irritating factors in the carotid sinus region.

The underlying physiologic disturbances responsible for the various manifestations of the hyperactive carotid sinus reflex appear to occur in the central neurons or in efferent arms of the reflex arc, not in the carotid sinus receptors. For this reason, surgical removal of the nerve connections of the carotid sinus region cannot be expected to relieve many cases, and whatever good results it may yield may not be permanent. It should be employed only in extremely serious cases of unconsciousness and convulsions which may be reproduced by the lightest pressure effect on the carotid sinus.

Inasmuch as very serious complications may develop as a result of the test in individuals with cerebral arteriosclerosis, great caution must be used in performing the test in such individuals.

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# PENICILLIN TREATMENT OF STREPTOCOCCAL PHARYNGITIS \*

By J. PHILIP LOGE,† M.D., *St. Louis, Missouri*, and EDWIN D. KILBOURNE,‡ M.D., *New York, N. Y.*

DURING recent years the commonplace and ubiquitous entity of "streptococcus sore throat" has been the object of intensive study. Interest in hemolytic streptococcal pharyngitis has been heightened both by its importance as an acute epidemic disease during the war, and by its current recognition as a primary excitant of rheumatic fever and glomerulonephritis. Coincidentally, the discovery of effective antistreptococcal agents has aroused interest in the treatment of the acute disease and the prevention of its sequelae.

The critical appraisal of any treatment demands the establishment of strict control groups and accurate delineation of the natural history of the disease in question. Survey of the current literature discloses no study of streptococcal pharyngitis in which a strict control group was established without regard for the severity of the presenting illness. Analysis of the course of the penicillin-treated disease has often been complicated by the concomitant administration of salicylates or sulfonamides.

An epidemic of streptococcal pharyngitis at a large, permanent army post provided an opportunity for the systematic study of the effects of treatment on the course of this disease. The epidemic was caused by group A hemolytic streptococci, largely types 19 and 23.§

During a 60 day period in the spring of 1947, 184 patients received a preliminary clinical diagnosis of streptococcal pharyngitis and were placed in special study groups at the time of their admission to the post station hospital. The objectives of the study were:

(1) To delineate the natural history of this epidemic of streptococcal pharyngitis in a young adult male population; (2) to assess the value of two methods of penicillin treatment as compared with purely symptomatic therapy; (3) to determine and evaluate the antistreptolysin response of patients in each of the three treatment groups.

The present report will be concerned mainly with the natural history and the results of treatment of streptococcal pharyngitis. Evaluation of the antistreptolysin response has been reported in a previous paper.<sup>1</sup>

*Plan of the Investigation.* The plan of the investigation together with a description of the bacteriological and serological methods used has been detailed in a previous article<sup>1</sup> and will be only summarized here.

\* Received for publication July 17, 1948.

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§ Typings were obtained on 80 patients (62.2 per cent); of these 56 were type 23 and 24 were type 19.

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*a. Selection of Patients.* One or both of the investigators personally examined in the hospital receiving office virtually all patients admitted with fever or complaints referable to the upper respiratory tract during a period when 516 cases of upper respiratory infection were admitted to the hospital. A preliminary clinical diagnosis of streptococcal pharyngitis was made in 184 cases, and these patients were assigned in approximate alternate rotation to one of several study wards. Notations of the pertinent physical findings were made by the authors on worksheets especially designed for this investigation. Patients who manifested a scarlatiform rash were considered to have a more serious disease (in agreement with Spink<sup>2</sup>), and were usually treated according to one of the two penicillin treatment schedules. They are not considered in comparing the untreated and treated groups, since most cases of scarlet fever received specific therapy.

At the beginning of the study 54 patients clinically diagnosed as streptococcal pharyngitis were treated with customary penicillin dosage consisting of 20,000 to 50,000 units every three hours for periods varying from four to seven days. Subsequently, the remaining 130 patients were dispatched alternately to one of two study wards; one group to receive penicillin, and the other, no specific treatment. With the exception of 11 patients with scarlet fever and two suffering from peritonsillar abscess at the time of admission, separation of patients into "treated" and "untreated" categories was effected without regard for the severity of the disease. Ward officers on the "untreated" wards were not permitted to initiate penicillin, sulfonamide, or salicylate therapy without consulting one of the investigators.

*b. Definitive Diagnosis and Selection of Patients.* A report by the Commission on Acute Respiratory Diseases<sup>3</sup> has implied that the definitive diagnosis of streptococcal pharyngitis is dependent upon the demonstration of anti-streptococcal antibodies during convalescence. In contrast, Rantz et al.<sup>2</sup> have stated that infection by streptococci cannot be excluded on the basis of the study of these antibodies (i.e. anti-streptolysin and antifibrinolysin) since 10 to 20 per cent of scarlet fever patients may fail to exhibit an antibody response. Studies by Weinstein and Tsao<sup>4</sup> and more recently by Kilbourne and Loge<sup>1</sup> have demonstrated that penicillin treatment of scarlet fever or streptococcal pharyngitis may prevent the usual antistreptolysin response observed in these diseases. Thus, an important criterion for the diagnosis of streptococcal disease is of limited use in the evaluation of patients treated with penicillin. The following, exacting criteria were established for the final inclusion of patients in the study to be presented, regardless of how "typical" the clinical picture had been at the time of admission. The criteria were: (1) fever greater than 100° F. on the day of admission; (2) predominating growth of beta hemolytic streptococci on the initial throat culture; and (3) an admission total leukocyte count greater than 10,000 cells per cu. mm.

The few cases which have been included which did not necessarily fulfill all three of these criteria were cases in which: (1) a significant antistreptolysin rise was demonstrated; (2) the patient had a scarlatinal rash; or (3) peritonsillar abscess from which streptococci were cultured existed at the time of admission.

Application of the criteria plus the loss of patients by transfer and incomplete laboratory data reduced the series from 184 to 127 patients. The high proportion of patients (84.3 per cent) in the "untreated" group who exhibited a significant antistreptolysin rise is evidence of the accuracy of the preliminary diagnostic impressions.

*c. Methods of Treatment. "Untreated" Group*—The patients in this group received symptomatic therapy in the form of hot saline gargles or irrigations, obligatory bed rest for three days, and codeine when necessary. Salicylates were specifically interdicted in order to permit accurate observation of fever duration. All patients were closely watched for the development of complications. Two who developed peritonsillar abscesses were started on penicillin therapy and eliminated from this group.

*"Treated" Groups*—The patients in these groups received the symptomatic therapy outlined above, including the obligatory period of bed rest. In addition, they received treatment with one of two penicillin regimens, which for convenience will be denoted penicillin I, and penicillin II.

*Penicillin I*—This schedule entailed a single daily injection of 300,000 units of penicillin in aqueous solution for six or seven days. This dosage was selected as an amount which would maintain detectable concentrations (more than .078 unit per c.c.) in the blood for five to seven hours, an appreciable fraction of the 24 hour period.<sup>5</sup>

*Penicillin II*—Patients in this group received penicillin in dosages comparable to usual experience: 20 to 50,000 units every three hours for from four to seven days. Most of the patients so treated (75 per cent) received penicillin for six or more days. The average period of therapy was 5.6 days, and the usual individual dose was 30,000 units. It was anticipated that this regimen would provide almost continuous effective blood concentrations against the hemolytic streptococcus. Rammelkamp and Kirby state that 20,000 units of penicillin "produce concentrations having maximal antistreptococcal action for a period of more than two-and-one-half hours with partially inhibitory levels for another one-and-one-half to two hours."<sup>6</sup>

*d. Laboratory Procedures.* The following studies were made of each patient, usually within 24 hours of admission: (1) total leukocyte count; (2) urinalysis; (3) chest roentgen-ray; (4) Dick test; (5) antistreptolysin titer; (6) throat culture.

The leukocyte counts were repeated on the fourth and ninth days, urinalysis and Dick tests on the ninth day; throat cultures on the fourth, ninth and twenty-first days, and the antistreptolysin titers were determined again on the twenty-first day following admission.

## OBSERVATIONS AND RESULTS

*The Nature of the Presenting Illness.* Hemolytic streptococcal pharyngitis as seen at Fort Monmouth in the spring of 1947 was an acute, febrile illness characterized almost invariably by throat soreness and frequently by moderate prostration. The illness was differentiated clinically from other endemic respiratory tract diseases by its more abrupt onset, the primary complaint of "sore throat," and the greater degree of prostration evident in its victims. Shaking chills and vomiting, although seen in less than one quarter of the patients, were evidences of toxicity of great value in differential diagnosis.

A surprising number of patients (82.9 per cent) complained of headache. This was usually frontal, but was sometimes occipital or generalized. Meningismus was occasionally simulated by posterior nuchal pain and soreness.

More than one-half of the patients complained of some degree of nasal congestion, but this was rarely a primary complaint. One-fifth of those with streptococcal pharyngitis suffered from pain in the extraocular muscles ("aching eyes"). Cough and hoarseness were rarely encountered.

Physical examination of patients in the receiving office was limited to measurement of the oral temperature, inspection of the skin, careful inspection of the pharynx, and palpation of the neck. Patients were usually seen on the first day of illness, as no penalty was attached to hospitalization.

and dispensary officers were ordered to hospitalize all febrile patients. Thus, the physical signs recorded below are truly indicative of the early acute disease.

Fever was usually present on admission, and exceeded 102° F. in almost 70 per cent of patients. Eighteen patients (14.1 per cent) presented themselves with scarlatiniform rashes. These cases were diagnosed as scarlet fever and are not utilized in this portrayal of the natural history of uncomplicated streptococcal pharyngitis. The incidence of rash varies with the erythrogenic potency of the infecting streptococcus<sup>7</sup> and therefore is a variable in any epidemic.

TABLE I  
The Natural History of Streptococcal Pharyngitis

Symptoms	%	No.*	Signs	%	No.*	Course (Untreated)	Days	No.*
Sore Throat	98.6	77	Pharyngeal Injection	100	83	Fever Duration	2.6	45
Headache	82.9	74	Fever	99.1	127	Local Symptom Duration	3.8	27
Prostration (moderate or severe)	59.9	44	Uvula Edema	86.7	83	Systemic Symptom Duration	3.8	30
Abrupt Onset	58.4	77	Cervical Lymphadenopathy	81.8	82	Physical Signs (duration)	4.1	20
Nasal Congestion	58.4	77	Cocexistent Cervical Adenitis and Tonsils	74.6	67	Pyogenic Complications	No. 4	51
Shaking Chill	26.0	76	Pharyngeal Edema	74.7	83	Late Sequelae	2	51
Aching Eyes	22.0	72	Tonsillitis (incidence of tonsils)	70.0	127	"Late Fever" (after febrile period)	11	45
Vomiting	17.5	74	Confluent Exudate	60.2	83	Reinfections or Relapses	0	51
			Scarlatinal Rash	14.1	127			

\* Indicates the total number of patients yielding adequate data relative to each point.

A cardinal sign was the cautious manner with which patients opened their mouths for examination, illustrating dramatically the *soreness* of the pharyngeal and peripharyngeal tissues. Pharyngeal injection was present in all patients, and was usually classified as being of moderate or severe intensity. The commonest sites of erythema were the soft palate and anterior pillars, and the tonsils, when present.

Obvious pharyngeal edema occurred in three-quarters of all patients and proved a valuable diagnostic sign. Edema of the uvula was present in more than 86 per cent of the group, and when pronounced, was almost pathognomonic of streptococcal infection. As emphasized by Rantz and his associates<sup>2</sup> it was found that edema and erythema are valuable and characteristic evidences of streptococcal pharyngitis.

Tonsillitis was noted in 70 per cent of the cases, and, as would be anticipated in the presence of contiguous pharyngeal infection, occurred in all patients with tonsils. In these patients diagnosis was aided by the more obvious erythema and edema, and the more extensive exudate.



Confluent exudate was observed in only 60 per cent of patients, although its presence is emphasized in classical descriptions of streptococcal sore throat. Cervical lymphadenopathy was a frequent finding (81.8 per cent) and was most often manifest in the tonsillar nodes. In the absence of tonsils, tender adenopathy was of value in differential diagnosis. It was not observed, however, that tonsils acted as a "barrier" to inflammation of the cervical tissues, as three-quarters of those with cervical adenitis had tonsils.

The signs and symptoms of the disease together with the course of the untreated illness are summarized in table 1.

### THE COMPARATIVE EFFECTS OF TREATMENT

The effect of three treatment schedules on the course of streptococcal pharyngitis will be compared with respect to the duration of the acute illness, the incidence of complications and late sequelae, the relapse or reinfection rate, and the persistence of the carrier state.

The duration of the acute disease can best be measured by determination of the persistence of symptoms and abnormal physical findings, including fever. In the present study, information regarding signs and symptoms was obtained by questioning and reexamination of the patients on approximately the fourth day of hospitalization (which was also usually the fourth day of illness) by one of the investigators. In an effort to obtain uniformity in the interpretation of signs and symptoms, reliance was placed only upon the observations or notations of the present investigators, except in the case of several of the earlier patients who received penicillin treatment II (see table 2).

In calculating the average duration of symptoms and signs, notations of i.e. "less than four days" have been given the mathematical value of four, spuriously implying an illness of longer than actual duration. In the small proportion of cases in which symptoms and signs persisted for more than four days, the exact duration of the illness was not determined, but such duration has been indicated merely as being "more than four days" (see table 2). Patients with protracted illness were categorized as having complications, sequelae or relapses of the acute disease and are discussed separately.

The comparative results of treatment are consolidated in table 2.

*Fever Duration.* The duration of the temperature response is probably the best single guide for determining the span of an acute febrile infection. Certainly, the frequency with which the body temperature is measured provides sharp definition of fever duration. Measurements of oral temperature were recorded usually four times daily, and occasionally every four hours. The duration of fever has been calculated and expressed in half days. Any day on which a temperature of greater than 98.6° F. has been recorded has been considered a day of fever unless such an elevation occurred only in the morning; in this event fever has been judged to persist for a "half

TABLE II  
The Comparative Effects of Treatment

	Untreated		Penicillin 1 (300,000 units q.d.)		Penicillin 11 (20-50,000 units q3h)	
		No.*		No.*		No.*
Fever Duration (days) (Patients with Rash) Fever Duration (days)	2.6 days	45	1.7 days	33	2.0 days	24
% with "Late Fever" (after 48 hr. afebrile period)	2.5 days	1	3.0 days	11	3.6 days	4
	24.4%	45	16.6%	30	7.4%	27
Duration of Local Symptoms (days)	3.8 days	27	3.4 days	24	(4.2)**days	29
% of Patients with Local Symptoms longer than 4 days	17.2%	29	8.7%	23	—	—
Duration of Systemic Symptoms (days)	3.8 days	30	3.4 days	22	(4.4)**days	29
% of Patients with Systemic Sym- ptoms longer than 4 days	3.5%	28	4.5%	22	—	—
Duration of Physical Signs (days)	4.1 days	20	4.3 days	18	—	—
% of Patients with Physical Signs longer than 4 days	37.0%	25	42.0%	19	—	—
Pyogenic Complications (number)	4	51	2	47	0	29
Late Sequelae (number)	2	51	3	47	0	29
Relapses or Reinfections (number)	0	51	2	47	3	29
% of Patients with Initial Leuko- cytosis	82.6%	46	93.5%	31	82.6%	23
% of Patients with Leukocytosis on 4th day	38.2%	34	25.8%	31	21.0%	19
Patients with Pred. Growth Beta Strep. on 1st Culture	100.0%***	47	100.0%***	40	100.0%***	27
% of Patients with Positive 4th day Culture	90.0%	40	37.4%	37	0.0%	19
% of Patients with Positive 9th day Culture	85.3%	41	53.5%	28	22.0%	9
% of Patients with Positive 21st day Culture	67.5%	37	35.2%	34	27.3%	22
% of Patients with Significant Anti- streptolysin Response	84.3%	51	63.8%	47	13.8%	29

\* Indicates the total number of patients yielding adequate data relative to each point.

\*\* See text. (Duration of systemic symptoms).

\*\*\* Does not imply that all patients had positive initial culture. Only those with positive initial cultures were used in following the bacteriology of the pharynx.

day." Afebrile periods of less than 48 hours have been counted as febrile days.

Inspection of table 2 reveals no marked differences in the average fever duration in the three groups of patients, although the tendency to a slightly shorter course in the penicillin-treated patients is obvious. Detailed analysis of temperature charts, however, disclosed important differences between penicillin-treated and untreated patients (figure 3). Defervescence occurred in two days or less in more than 93 per cent of patients receiving intermittent

penicillin in large doses (penicillin I), and in almost one-half of this group (46.6 per cent) the pyrexia lasted but one day. More than two-thirds of the group treated with penicillin II were afebrile before the third day, but only 40 per cent of untreated patients.

In most cases fever had terminated by the fourth day, even in the untreated. It will be demonstrated that this day marks the usual limit of the illness as judged by the duration of symptoms and signs other than fever.

The greater length of pyrexia in patients with rash (figure 4) is justification for their separate consideration elsewhere.

*Late Fever.* A finding of conjectural significance was the occurrence of sporadic, low-grade temperature elevations during the convalescence of some patients. These transient "late fevers" followed the initial febrile phase of the acute infection by at least 48 hours, and were not associated with other evidences of relapse. The majority of such delayed fever reactions were manifested by only two or three recorded elevations of temperature. Late fever was present in one-quarter of the "untreated" patients, and one sixth of those treated by intermittent penicillin injections (penicillin I). It was uncommon in the group (penicillin II) treated with frequent injections of penicillin (only one-twelfth of patients).

Rantz and his associates<sup>8</sup> noted recrudescent fever unassociated with evidence of local pyogenic disease in 14 convalescent victims of streptococcal pharyngitis. In contrast to patients in the present series, these individuals usually suffered severe malaise. Electrocardiographic evidence of carditis and prolonged elevation of the erythrocyte sedimentation rate were noted in several of the patients in Rantz's study, leading him to the conclusion that late fever was a non-suppurative manifestation of the "post-streptococcic state" analogous to arthritis and carditis.

*Duration of Local Symptoms.* The complaints of "sore throat" and pain on deglutition were considered to be logical indices of the persistence of pharyngeal cellulitis. Other symptoms indicative of upper respiratory tract inflammation are nasal congestion, stiff neck, and otalgia. Patients were questioned with respect to the duration of such symptoms on the fourth day of hospitalization. The majority of patients, regardless of treatment, were free of complaints by the fourth day (table 2). It should be noted, however, that 17.2 per cent of patients receiving only symptomatic treatment experienced local symptoms after this time. Such symptoms were usually mild unless classed below as complications.

*Duration of Systemic Symptoms.* The term "systemic symptoms" includes all complaints not immediately referable to the upper respiratory tract, such as headache, malaise, chilliness and myalgia. Again, no important differences were noted in the duration of such symptoms in the three groups. There was a close parallelism between the duration of local and systemic complaints. The proportion of patients with systemic complaints after four days was very small, and approximately of the same extent in the three treatment groups. The apparent greater duration of symptoms in the

group treated with penicillin II is more probably related to the infrequency of chart notations than any failure of this regimen, because, as stated before, data relative to several members of this group were unconfirmed personally by the present investigators.

*Duration of Physical Signs.* The persistence of such signs as pharyngeal injection, edema, and exudate was noted on the fourth day of illness. Despite the early subsidence of local symptoms, approximately two-fifths of patients in both control and penicillin-treated groups had residual signs of pharyngeal infection on the fourth day. The average duration of such signs was about four days in the two groups subjected to careful observation (table 2).

*Pyogenic Complications.* Peritonsillar abscess was the commonest complication observed. Two "untreated" patients and two patients receiving intermittent penicillin (penicillin I) developed this condition. The group treated with frequent injections was notably free of pyogenic complications of the acute disease.

Two cases of acute purulent paranasal sinusitis diagnosed in the group receiving symptomatic treatment have been included as pyogenic complications, although sinusitis may be considered as an incidental part of the acute disease.

Purulent otitis media was not observed in this series.

*Late Sequelae.* All patients were followed for at least 21 days, and repeat throat cultures and blood for antistreptolysin titers were obtained at the end of that period. Most patients were assigned to the post for at least six months, during which time late effects of streptococcal infection should have become apparent, particularly because current policy dictated the hospitalization of all patients with fever.

Two patients developed obvious rheumatic fever, while another incurred arthralgia, prolonged fever, and elevation of the red blood cell sedimentation rate without developing the physical signs of redness or swelling of his joints. These three cases occurred in the group treated with large daily doses of penicillin (penicillin I). In the untreated group, one patient experienced prolonged fever (19 days), and another manifested microscopic hematuria on a single occasion, but showed no other evidences of nephritis.

The 29 patients treated with continuous penicillin dosage (penicillin II) apparently remained free of sequelae.

*Relapses or Reinfections.* Five patients experienced clinical relapses associated with the reappearance of beta hemolytic streptococci in predominant growth on pharyngeal culture. The reappearance of disease may have been true relapse caused by the original invaders, or may have represented "reinfection," or invasion by streptococci of another serologic type. Data on this question are not available. Two recrudescences, which occurred in the group treated with penicillin I, became evident on the third day after the cessation of therapy, whereas the three recurrences noted in the

group treated with penicillin II were delayed until the seventh, thirteenth, and twenty-first days after the discontinuation of treatment.

It may be significant that all patients who suffered recurrence of infection had been given antibacterial therapy. No relapses occurred in the control group. The statistical significance of this observation in the present series may be subject to challenge, but when it is correlated with the findings of others (Plummer et al.<sup>9</sup>; Rantz, Boisvert, and Spink<sup>10</sup>) it is strongly implied that relapse rates are higher in groups receiving penicillin treatment. In an early communication on penicillin therapy in hemolytic streptococcal pharyngitis, Plummer and his co-workers<sup>9</sup> noted clinical and bacteriological relapse 48 hours after cessation of therapy in four of nine patients treated

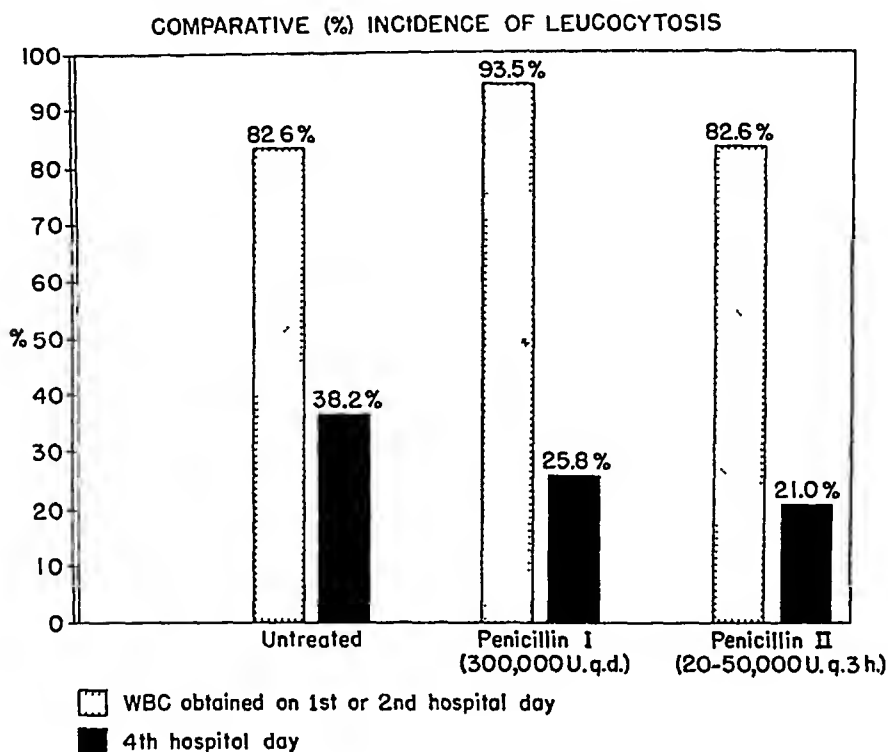


FIG. 1.

with penicillin for three or four day periods. Rantz et al.<sup>10</sup> described frequent bacteriological and clinical relapses in patients treated with either "short course(s)" (32 to 64 hrs.) or "long course(s)" (80 hrs.) of penicillin administered at four hourly intervals.

The immunological implications of these data will be discussed subsequently.

*Duration of Leukocytosis.* The infrequent determination of the total leukocyte counts makes this finding of little value in precise measurement of the duration of acute pharyngitis. However, comparison of the percentage incidence of leukocytosis on the initial and fourth day determinations adduces further evidence for the brevity of the disease process in all three groups

of patients (figure 1). Furthermore, significantly fewer penicillin-treated patients had abnormal total leukocyte counts on the fourth day than members of the "untreated" group.

*Antistreptolysin Response.* The antistreptolysin response of patients in the three treatment groups has been presented in detail elsewhere.<sup>1</sup> In summary, 84.3 per cent of untreated patients manifested a significant rise in the antistreptolysin titer; and in comparison, 63.8 per cent of those treated with large daily injections of penicillin (penicillin I), and only 13.8 per cent

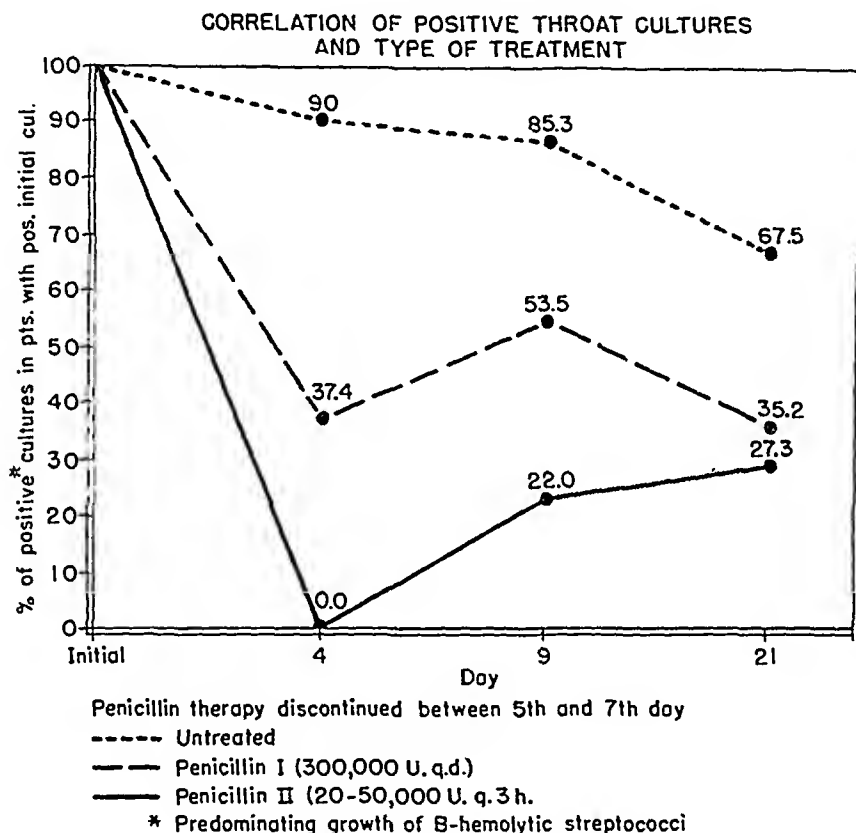


FIG. 2.

of patients who received small intermittent doses of penicillin (penicillin II) showed an antistreptolysin response (figure 3). The average amplitude of response paralleled the incidence of response, and was greatest in the untreated group, and least in patients treated with the schedule, penicillin II.

*Duration of the Carrier State.* Cultures of the posterior pharynx and tonsils were obtained on all patients at the time of admission, and were repeated thereafter on approximately the fourth, ninth, and twenty-first days following hospitalization. The results of this bacteriological survey are illustrated graphically in figure 2. It will be observed that bacteria disappeared gradually from the throats of patients in the control series, and that

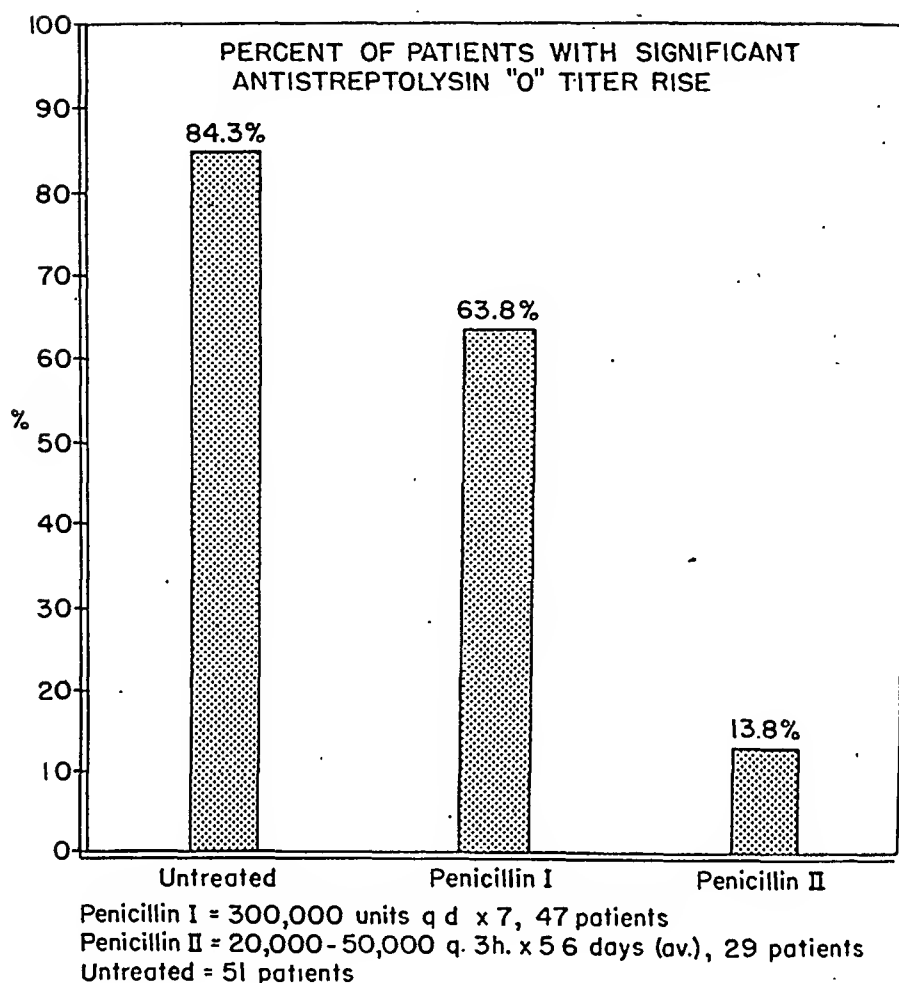


FIG. 3.

TABLE III  
The Comparative Durations of Fever

Days	Untreated	Penicillin I	Penicillin II
1	9.3%	46.7%	8.7%
1½	16.3%	10.0%	30.4%
2	16.3%	33.4%	30.4%
2½	21.0%	3.3%	8.7%
3	11.6%	3.3%	17.4%
3½	7.0%	0	0
4	11.6%	0	4.4%
4½	2.3%	3.3%	0
5	2.3%	0	0
5½	0	0	0
6	2.3%	0	0
	100.0% (43)*	100.0% (30*)	100.0% (23*)

Penicillin I = 300,000 units q.d.  
 Penicillin II = 20-50,000 units q.3 h.

\* Indicates number of patients.

more than two-thirds of these patients still carried streptococci in predominating growth after 21 days or more.

In contrast, a prompt decline in the incidence of positive throat cultures was evident on the fourth day in both penicillin-treated groups. In fact, cultures were uniformly negative in patients in whom continuously effective blood concentrations of penicillin had been maintained (penicillin II). The interesting direct relationship between the percentage of positive fourth day cultures and the incidence of antibody response will be discussed.

TABLE IV

Comparative Durations of Illness in Patients with and without Rash

Duration in Days	With Rash	Without Rash
Fever	2.9	1.7
Local symptoms	4.2	3.4
Systemic symptoms	4.5	3.4
Physical signs	4.1	4.3

All treated with penicillin I (300,000 units q.d.)

Cultures obtained on about the ninth day represented the first post-treatment cultures. The incidence of positive cultures continued to decline in patients who had received no antibacterial therapy, but increased in both penicillin-treated groups following the cessation of therapy.

By the twenty-first day, the incidence of positive cultures had continued to increase to a peak of over 27 per cent in patients treated with penicillin schedule II, but had declined in the control group and in the group treated with penicillin schedule I (large daily doses), to lower incidences than noted on previous cultures.

### SCARLET FEVER

Eighteen patients had cutaneous eruptions of sufficient extent and duration to justify the diagnosis of scarlet fever. In nine cases the offending streptococcus was type 19, in three, it was type 23, and in six cases, typings were not obtained. Twenty-four illnesses in the total series were caused by type 19, whereas type 23 was responsible for 56.

The bulk of current opinion favors the concept that scarlet fever is merely streptococcal pharyngitis with rash (Rantz and Boisvert<sup>2</sup>). Certainly, there is no important epidemiological difference between the two diseases. In the absence of uniformity of opinion on this point, patients with rash will be considered separately for the purpose of comparison with other studies. As indicated before, no controls are available for the evaluation of treatment effects in this group.

One symptomatically-treated patient experienced 2.5 days of fever, was a carrier of streptococci on the twenty-first day, and developed an anti-streptolysin response.

Six patients were treated with penicillin schedule II. Fever averaged 2.5 days in duration, and patients suffered no complications, sequelae, or



relapses. None were carriers on the twenty-first day, and none manifested rises in antistreptolysin titer.

Eleven patients were treated with penicillin schedule I (300,000 units once daily). Data relative to these patients are summarized in table 3, and compared with data concerning patients without rash in the same treatment group. The small number of patients with rash mitigates against accurate comparison, but no striking difference in the durations of illness is evident. In this group no complications, but one relapse and one case of rheumatic fever occurred; about one-half showed antibody response, and four were carriers on the twenty-first day.

### DISCUSSION

*The Acute Disease.* Penicillin, whether given in continuous or intermittent dosage, did not significantly modify the symptomatology of hemolytic streptococcal pharyngitis, but did reduce the period of pyrexia and leukocytic reaction. The shorter mean duration of fever in penicillin-treated patients was not paralleled by shorter periods of throat pain or abnormal physical signs than were observed in symptomatically-treated patients.

The rapid elimination of most of the infecting organisms by penicillin probably obviates prolongation of the host defense reactions of pyrexia and leukocytosis. Subsidence of local pharyngeal inflammation is understandably slower. The early and frequent relapses noted when penicillin is discontinued after one to three days<sup>9, 11, 12</sup> are evidence that reduction of the number of streptococci in the throat and tonsils is not complete nor immediate. It is possible that sufficient bacteria remain to perpetuate the local pathological process, but are inaccessible to routine cultural procedures. Furthermore, the brevity of the acute disease tends to minimize differences of reaction within its usual three day span. This factor probably explains in part the failure of penicillin to shorten the duration of systemic symptoms.

*Pyogenic Complications.* Few pyogenic complications were observed in this study of 127 patients. As might be anticipated, four untreated patients suffered extension of the local pyogenic process, whereas none of the patients who received penicillin in conventional dosage (penicillin II) were so affected. Two of 47 patients who received 300,000 units once daily (penicillin I) developed peritonsillar abscesses. It is notable that elimination of streptococci was less rapid in this group than in patients treated with penicillin II. However, the total number of patients was less in the latter group so the differing incidence of complications in the penicillin treated groups may not be of significance. The value of penicillin in conventional dosage is well established. Hirsh and his associates, in a study of the treatment of scarlet fever, found that penicillin therapy resulted in a "decided reduction in the incidence of pyogenic complications"<sup>12</sup>; and a similar investigation by Hoyne and Brown<sup>13</sup> resulted in a similar conclusion. In patients who are not under constant surveillance, the use of penicillin in

streptococcal pharyngitis appears justified, if only from the standpoint of the prevention of pyogenic extension of the disease.

*Late Sequelae.* No late sequelae of streptococcal infection occurred in patients in whom effective blood concentrations of penicillin had been continuously maintained for four to seven days (i.e.: penicillin II). In this group of patients, elimination of streptococci was more rapid, and antibody response (antistreptolysin) was minimal in incidence and degree (figure 2).

Three cases of rheumatic fever followed treatment with intermittent penicillin therapy (penicillin I). In this group over 60 per cent of patients showed an antibody response, and a higher percentage of patients maintained hemolytic streptococci in their throats than in the former group. It is of interest that all three cases developed rises in antistreptolysin titer, either prior to or coincident with the appearance of rheumatism. Two patients on symptomatic therapy developed late sequelae. Both manifested rises in antistreptolysin titer.

The occurrence of high antistreptolysin titers in patients with acute rheumatic fever has been frequently observed.<sup>14</sup> This phenomenon was originally described by Todd<sup>15</sup> and adduced as evidence that rheumatic fever was a sequel to streptococcal infection. The correlation between antistreptolysin response and rheumatic activity was subsequently noted by Coburn and Pauli<sup>16</sup> in the study of an outbreak of streptococcal pharyngitis in a home for rheumatic children. They reported that 14 rheumatic subjects out of 16 exposed developed acute rheumatic exacerbations accompanied by rises in antistreptolysin titers, following infection. Weinstein and Tsao's recent study of scarlet fever patients<sup>4</sup> disclosed that all subsequent cases of rheumatic fever occurred in patients who developed rises in antistreptolysin titer.

The conception of rheumatic fever as an allergic reaction to the hemolytic streptococcus has led to a search for a sensitizing antibody. In a recent paper Rantz and Randall<sup>17</sup> described an unidentified "anti-x antibody" which occurred more frequently in patients developing arthritis than in uncomplicated streptococcal pharyngitis.

There is no evidence that antistreptolysin is directly related to the rheumatic allergic state. It is, however, an easily measurable antibody demonstrable in 78 to 90 per cent<sup>18</sup> of streptococcal infections. Evidence has been cited that the incidence of this antibody response is diminished by penicillin therapy.<sup>1, 4</sup> One may speculate that treatment which prevents the formation of one streptococcal antibody may suppress the production of others, including the sensitizing antibody of rheumatic fever. Interference with antibody formation by penicillin is most logically related to the early removal of the antigenic streptococcus (figure 2). Dowling and Hirsh remarked that penicillin quickly reduced the "toxicity" in scarlet fever, without neutralization of the erythrogenic toxin.<sup>19</sup> These investigators believe that the apparent antitoxic effect of penicillin results indirectly from the rapid elimination of the organisms producing toxin. The present authors noted persistence of a positive Dick test in two patients with scarlet fever treated

with penicillin. Pursuant to this reasoning, it is of interest that two rheumatic subjects treated immediately with penicillin for acute streptococcal infections developed no increases in antistreptolysin titers, and no recrudescences of rheumatic fever (Goerner, Massell, and Jones<sup>20</sup>). Controlled studies of large rheumatic populations are needed for the evaluation of these preliminary observations.

*Relapses or Reinfections.* The five relapses noted in this group of 127 patients occurred in penicillin-treated patients. The frequent relapses observed in penicillin-treated patients in other series has been commented upon. In three patients in the present series (all treated with continuous penicillin therapy) it was established that prior to the second illness no antistreptolysin response had occurred. In two of these patients who received no antibacterial therapy during the recurrence, significant antistreptolysin responses then occurred.

It is suggested that the coincidence of diminished antibody formation and greater relapse rates in penicillin-treated patients may be related to the early reduction in streptococci (without their complete extirpation) thus preventing the development of natural immunity.

*The Carrier State.* Penicillin treatment greatly lessened the incidence of positive cultures observed at the twenty-first day, whether administered in daily or three-hourly injections. The epidemiological implication of this observation is obvious. It must be pointed out, however, that in a group of scarlet fever patients followed carefully by Rubenstein and Foley<sup>21</sup> a period of "cultural latency" occurred in sulfonamide treated patients which apparently had *no significant effect on the incidence of late secondary cases*. In approximately half these cases it was noted that the original streptococcus reappeared in the cultures after an interval of one to five weeks. In the present study, the incidence of positive cultures in patients treated symptomatically or with penicillin schedule I showed progressive decline, in contrast to the progressively increasing positive cultures noted in patients who had received frequent injections of penicillin. One is tempted to relate this phenomenon to the diminished antibody formation in this latter group.

#### SUMMARY

1. The natural history and results of treatment of 127 cases of streptococcal pharyngitis and scarlet fever have been presented and discussed.
2. The comparative effects of symptomatic treatment and therapy with two penicillin regimens were studied with reference to the course of the acute disease, the incidence of pyogenic complications, late sequelae, relapses, the carrier state, and antistreptolysin formation.

#### CONCLUSIONS

1. Penicillin therapy does not significantly modify the symptomatology of streptococcal pharyngitis, but shortens the mean duration of fever and leukocytosis.

2. Penicillin administered by frequent injections in conventional dosage (20,000 to 50,000 units) probably reduces the incidence of pyogenic complications.

3. Penicillin therapy reduces the incidence and degree of antibody response as measured by the antistreptolysin titer. This interference with the antibody mechanism is less marked in patients treated with large single daily doses of penicillin.

4. The suppression of antistreptolysin response by penicillin is probably mediated by early reduction of the number of streptococci in the pharynx.

5. Penicillin therapy reduces the incidence of pharyngeal carriers observed at the end of three weeks.

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# CASE REPORTS

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## RENAL DWARFISM WITH HYPERPARATHYROIDISM IN A CASE OF CONGENITAL FAMILIAL MALFORMATION OF THE KIDNEYS \*

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THE clinical picture of dwarfism in children, with or without rickets, in combination with pathological states of the kidneys, has been observed and reported fairly frequently in the last decades, after it had been recognized as a clinical entity by Fletcher (1911).<sup>13</sup> Descriptions and discussions of this condition are given in a number of monographs and textbooks on children's diseases,<sup>30, 32</sup> bone diseases,<sup>40</sup> kidney disorders,<sup>41</sup> as well as in textbooks on pathology and clinical physiology. However, the condition is a rare one, and some of its principal features, especially with regard to its etiology, are not yet fully clarified.

In short, renal dwarfism consists of stunted growth, retardation of sexual development, but in most cases normal mental development, combined with symptoms of renal impairment, such as polyuria, isosthenuria, hyposthenuria, presence of albumin and pus cells in the urine, and progressive uremia. Other related features are increasing weakness, anemia, dry and coarse skin with yellow pigmentation and multiple brown spots. Hypertension and changes in the eye fundus are usually absent. In the last decade a number of cases have been reported in which a marked hypertrophy of the parathyroid glands was found at autopsy; in some cases (Shelling and Remsen<sup>38</sup>) the hyperactivity of these glands could be demonstrated during life by the method of Hamilton and Schwartz.

The retardation of growth is often, but not always, combined with skeletal deformities, not unlike those of rickets, which are referred to by the former designation of the condition as "renal rickets." Other names of this disease are "osteonephropathy" and "renal osteodystrophy," stressing the connection between the renal and the osseous changes, while the names "renal osteitis fibrosis cystica" and "renal hyperparathyroidism with osteoporosis fibrosis cystica" are designed to express a definite opinion on the cause of the frequently present changes in the bone structure and their connection with the parathyroid glands.

The kidney lesion which is found in these cases is either of the inflammatory type (glomerulonephritis or interstitial nephritis) with progressive destruction of the functional tissue, or it is of the type of renal malformation, with or without obstruction of the urinary passages, and in many cases with superimposed ascending infection of the renal tissue. This latter type has attracted in the last few years the special interest of urologists to the syndrome of renal dwarfism (Howard<sup>19</sup>; Charnock<sup>4</sup>; Harrison<sup>17</sup>; Hayward<sup>18</sup>; Hughes and Gislason<sup>20</sup>), as these

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cases seem to be amenable to prevention and therapy by early recognition of the underlying disorder and by surgical correction of the obstruction. According to the literature, the cases of renal dwarfism combined with the congenital type of renal disorders seem to prevail among the total number of cases (Ellis and Evans<sup>10</sup>; Hamperl and Wallis<sup>18</sup>; Anderson<sup>3</sup>).

According to the opinion of most of the observers, especially as reported in the Anglo-American and Scandinavian literature, there is no doubt as to the causal relationship between the bone disorder and the disease of the kidneys. These authors base their views on the assumption that the skeletal changes usually appear at a much later date than the kidney lesions, at a time, indeed, when impaired kidney function has already caused a severe disturbance in the mineral metabolism of the body and its fluids. This time relation granted, it still remains to be defined what is the exact character of the causal relationship, as well as the rôle of other abnormalities, especially the hyperplasia of the parathyroid glands, in the chain of events.

It is well known (Mandl<sup>26</sup>; Albright,<sup>1</sup> and many others) that primary hyperparathyroidism, caused by a tumor of one or more of the parathyroid glands, may lead to bone changes (osteitis fibrosa, osteoporosis), and to metastatic calcinosis in the kidneys, with impairment of the renal function, and it is not unlikely that some of the cases described as "renal rickets" were really cases of primary hyperparathyroidism with secondary skeletal changes and renal damage.

On the other hand it has been shown (Pappenheimer and Wilens<sup>31</sup>) that experimental reduction of renal tissue in rats and longstanding nephritis in man, even in adults, leads to decalcification of bones and to hypertrophy of the parathyroid glands. This mechanism, initiated by the insufficiency of the kidneys, is claimed as effective in the genesis of renal dwarfism by practically all those observers who maintain a causal relationship between the kidney disorder and the skeletal changes. In addition to this mechanism it may happen that the secondarily hypertrophied parathyroids act like primary tumors of these glands and lead to calcification and additional damage in the kidneys.

The precise mechanism by which the renal insufficiency exerts its influence on the bones and the parathyroid glands has been the subject of many discussions and of experimental investigations. Some authors (Parsons<sup>33</sup>; Mitchell<sup>28</sup>; Drake, Albright and Castleman<sup>9</sup>) regard the retention of phosphate by the damaged kidneys as the decisive chemical factor, and it has been shown experimentally (Pierre and co-workers<sup>34</sup>) that hyperphosphatemia causes increase in weight of the parathyroid glands. Other observers (Albright, Drake and Sulikowitch<sup>2</sup>; Ham<sup>15</sup>; Kaijser<sup>22</sup>) believe that the hypocalcemia caused by the increased excretion of calcium-phosphate through the intestines is the main factor, while by many (Jaffe, Bodansky and Chandler<sup>21</sup>; Mach and Rutishauser<sup>25</sup>; Graham and Oakley<sup>14</sup>; Snapper<sup>40</sup>; Tomenius<sup>41</sup>) the chronic acidosis of renal insufficiency is held responsible. The retardation of growth is explained by some authors (Danis and Rossen<sup>6</sup>; Smyth and Goldman<sup>39</sup>; McConney<sup>27</sup>) by the "antigrowth factor of the parathyroids" of Thompson.<sup>36, 42</sup>

This interpretation of the causal interrelationship between the kidney changes and the bone deformities, well founded as it seems to be in a great many cases, does not fit all the reported instances of renal dwarfism. Especially it leaves unexplained those numerous cases in which the skeletal changes consist only in stunted growth, without marked decalcification or rickets-like deformities, and

those in which the above mentioned time relation between the appearance of the kidney lesions and the bone changes cannot be demonstrated. Those cases clearly demand a different explanation which may be found in the direction indicated especially by French and German authors. Nobécourt and Kaplan (1934)<sup>30</sup> designate as unauthorized the conclusion "that the statural hypotrophy and the dwarfism, associated with affections of the kidneys and urinary passages, are caused by the latter" ("rien n'autorise à conclure . . . que l'hypotrophie staturale et le nanisme, associés à des affections du rein ou des voies urinaires, en soient la conséquence"). Debré and co-workers (1937)<sup>7</sup> clearly express the same view, but they accept the "phosphatemia-theory" of Parsons and Mitchell for some cases which actually present primary renal insufficiency and secondary rickets-like bone changes. The explanation offered by these authors as well as by the German observers of this condition (Loeschke<sup>24</sup>; Hamperl and Wallis<sup>16</sup>) is that the dwarfism or infantilism and the malformations of the urinary tract are parallel, but not interdependent expressions of congenital disturbances. Loeschke<sup>24</sup> cites as proof for this theory a case of dwarfism combined with severe malformations of the urinary passages, but without any signs of diminished ability of the excretory functions of the kidney. Further proof for this explanation may be found in the frequent occurrence of other congenital malformations or functional disorders in cases of renal dwarfism, for instance in the combination with hypochloremia and glycosuria (Fanconi<sup>11</sup>; de Toni<sup>8</sup>) or with abnormalities in the cystine metabolism (Lignac<sup>23</sup>). All these disturbances may be regarded, according to Rule and Grollman,<sup>37</sup> as belonging to one clinical syndrome.

As to the question of a common, possibly endocrine factor for all these abnormalities, most of the French and German authors as well as some English and American authors (Chown<sup>5</sup>; Anderson<sup>3</sup>; Price and Davie<sup>35</sup>; Moehlig<sup>20</sup>) point to the pituitary gland (and the diencephalic region) as the probable seat of the primary congenital disturbance.

The following case is reported as an example of renal dwarfism with hyperparathyroidism, but without severe bone changes, in which the renal disorder as well as the retarded growth was observed from earliest infancy, both of them probably resulting from a congenital disturbance. Moreover, this case seems to be of particular interest as the kidney disorder was not only congenital but also familial, and of a kind which apparently has not yet been described in the literature.

#### CASE REPORT

The patient, S. S., a girl 13 years of age, was sent to the outpatient department by a school nurse who, during a routine examination, had found albumin in her urine. Because of the visible retardation of growth, a connection of this with some underlying kidney disorder was suspected and the girl was admitted to the hospital for a thorough examination.

The girl's mother, M. S., was a patient of the same department seven and four years previously. She was suffering from "congenital anomaly of the kidneys, pyelitis and chronic nephritis," and died in January 1940 from "uremia and septicemia." It was noted that she was of small stature, but otherwise she showed no malformations. Her age at the time of death was 35. Figure 2 shows the pyelogram which was taken from this patient. The methylene blue excretion of the right side was delayed and very poor.



One elder sister of our patient, L. S., was examined in 1942. The girl was at that time 18 years old, but gave the impression of an underdeveloped girl of about 15 years. According to information received from her father, she had always been somewhat delicate and underweight, but showed no other abnormalities. In 1942 her urine contained traces of albumin and many pus cells. The same findings were present in April 1944. At this time her blood pressure was 120 mm. Hg systolic and 60 mm. diastolic. The chemical analysis of her blood showed 17.5 mg. per cent urea, 3.5 mg. per cent uric acid, 11 mg. per cent calcium, 4.5 mg. per cent phosphorus and 11 units



FIG. 1. The patient (right), S. S., at the age of 14½ years, together with a girl of the same age.

phosphatase. The kidneys were examined by methylene blue excretion and retrograde pyelography. The right kidney showed retarded dye excretion. The pyelogram (figure 3) showed a hypoplastic kidney on the right side, resembling the malformation found in her mother, M. S., and her sister, S. S.

History: Our patient had had abnormal urinary findings since early infancy, and had also shown marked retardation of growth observable in the first year of her life. At the age of one and one-half years she was smaller than another girl of the same family who was then only six months old. She continued, however, to grow and her mental development was quite normal. She attended school according to her age.

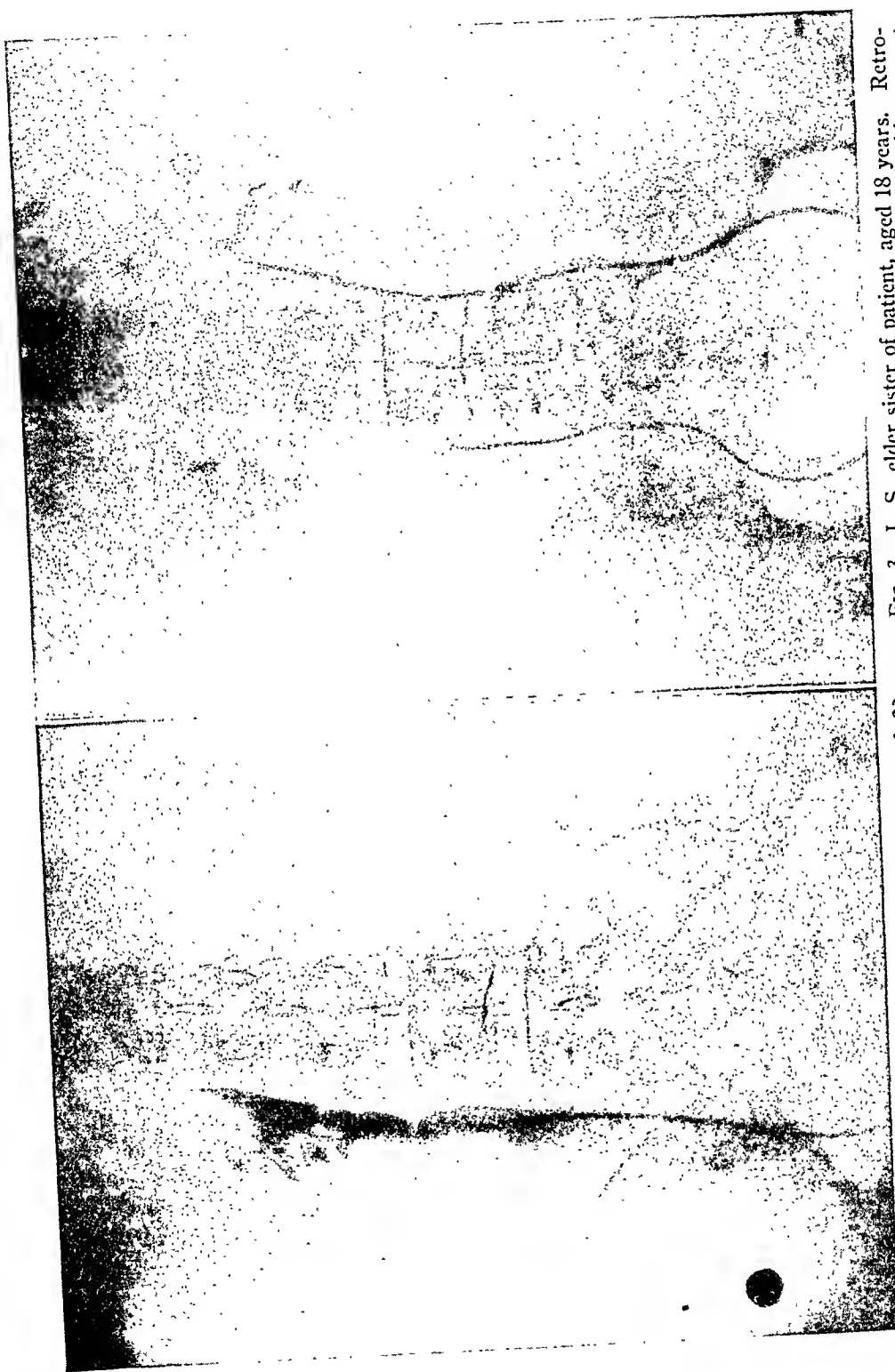


FIG. 2. M. S., mother of the patient, at the age of 32. Retrograde pyelography of the right kidney: Dilatation of the pelvis and of the calices, the upper calix elongated, in straight line with the ureter. The other calices are short and blunt. The ureter appears as a dilated inelastic tube. (The left kidney and ureter were normal by excretory urogram.)

FIG. 3. L. S., elder sister of patient, aged 18 years. Retrograde pyelogram. The right kidney has a small thin amount of renal parenchyma, the pelvis is small, the calices are short and blunt, with little renal tissue between them. Note compensatory hypertrophy of the left kidney, with large amounts of renal tissue.

In April 1940, at the age of 10 years, she was examined by a urologist (Dr. W. Nissel). His findings revealed an underdeveloped girl, but general examination was normal. The urine contained many pus cells. Cystoscopic examination showed normal bladder and ureteral openings. Methylene blue, after intravenous injection, appeared on the left side after five minutes, on the right side after seven minutes. Ureteral catheters passed on both sides without difficulties. Ureteral urine contained pus cells, right more than left. Intravenous pyelography was attempted but did not visualize the kidneys. For retrograde pyelography see figure 4.

During the following years her health chart contained repeated observations on general weakness, low specific gravity of the urine, with findings of albumin and pus cells. In November 1940, at the age of 10 years, her height was 117 cm., and her weight 19.3 kilograms, the normal figures for this age being 128 cm. and 26 kg. respectively. In October 1942, about one year before her first hospitalization, her blood urea was 85 mg. per cent.

TABLE I  
Blood Findings during the First Stage (Chronic, Latent Renal Impairment)

Date	Urea mg. %	Uric Acid mg. %	Sugar mg. %	Cal- cium mg. %	Phos- phorus mg. %	Phos- phatase Units	CO <sub>2</sub> Vol. %	Total Prot. gr. %	R.B.C. Mil- lions	Hgb. %	W.B.C.
Oct. 27, 1942	85								4.03	72	
Dec. 26, 1943	175	6.05							3.8	65	10,200
Dec. 27, 1943	196										
Dec. 30, 1943				10.3	5.1	5.9					
Jan. 6, 1944				10.5	5.6	4.4					
Feb. 8, 1944	122.5						30.9				
May 29, 1944	91	6.35	78								
Aug. 7, 1944	77	5.8							4.0		6,000
Sept. 16, 1944	147	6.2		9.8	6.1			7.45	3.09	60	5,100

On admission to hospital, in December of 1943, the physical examination showed a somewhat pale and undernourished, but otherwise normal girl, of an apparent age of eight or nine years, her real age being 13½ years. Her height was 131 cm., her weight 22 kg., instead of about 145 cm. and 36 kg. According to the classification of Wetzel<sup>43</sup> she belonged to group B<sub>4</sub> ("poor"), with development of 55 units, corresponding to a normal child of seven and one-half years. She showed no secondary sex characteristics and had not begun to menstruate. Her skin was dry, pale, and showed a yellowish tinge. The hair was also dry and lacked the normal luster. The girl was mentally alert; her intelligence and her interests were those of her actual age. She did not complain of anything and the physical examination did not reveal any abnormal findings. Her blood pressure was 110 to 130 mm. Hg systolic and 80 to 100 mm. diastolic. The eye fundi were without pathological changes. Dental examination showed calcification, dentition, and development of teeth to be normal and in accordance with her age. Basal metabolism was + 5 per cent.

Laboratory examinations: Red blood cells 3.8 millions, hemoglobin 65 per cent, white blood cells 10,200 per cu. mm., with a normal differential count. Urinalysis:

specific gravity 1.004 to 1.007, albumin ++++. In the sediment there were many pus cells and some red cells present. Urine culture revealed *Bacillus coli*.

At that time her blood urea was 175 to 196 mg. per cent. For other chemical findings in the blood see table 1.

Roentgenographic examination of heart and lungs was normal. Skeleton and skull were without visible decalcification or deformities. The kidneys could not be visualized by intravenous pyelography; retrograde filling showed the same picture as in figure 4.



FIG. 4. S. S., the patient, at the age of 10 years. Retrograde pyelography. Right kidney: Small pelvis with rudimentary deformed calices. Left kidney: Slightly dilated pelvis and calices. Overdistention of both ureters. (The plain roentgen-ray picture showed a very small right kidney in contrast to a large kidney shadow on the left side.)

On the basis of the history and the clinical and laboratory findings a diagnosis was made of renal dwarfism, represented by retardation of growth and development, in connection with a congenital abnormality and chronic inflammation of both kidneys.

During the following period the patient was seen and examined from time to time. For about one year her condition was essentially unchanged as far as the kidney function and general symptoms were concerned, but, on the other hand, there was from this time on a complete arrest of her development and the retardation, relative

TABLE II  
Blood Findings during the Terminal State (Severe, Manifest Renal Insufficiency, with Hyperphosphatemia and Acidosis)

Date	Urea mg. %	Uric Acid mg. %	Sugar mg. %	Calcium mg. %	Phos- phorus mg. %	Phos- phatase Units	CO <sub>2</sub> Vol. %	Total Protein gr. %	Albumin gr. %	Globulin gr. %		R.B.C. Millions	Hgb. %	W.B.C.
Feb. 8, 1945	315	6.6	110		8.9		17.6							
Feb. 16, 1945	438	7.0					14.7				Creatinin +++			
Feb. 19, 1945	455			10.4	12.1	10.2		8.55	6.1	2.45				
Feb. 23, 1945												2.88		8,600
Feb. 26, 1945	385				13.8	10.3	42.4	8.86	5.8	3.06				
March 5, 1945	437	7.5		9.3	13.6		38.2							
March 12, 1945	458	8.5		12.8	10.0		32.0							
March 15, 1945	445						37.6							
March 21, 1945	500						30.9	8.15					40	
March 27, 1945												1.22		18,600

to her age, became more prominent. Figure 1 shows the patient together with another patient of the same age.

In February 1945 she was again hospitalized. At that time she had begun to feel rather weak, suffered from headaches and vomited frequently. Her skin was dry, scaly and more yellow than previously, with numerous brown spots, especially on the face and on the forearms. The laboratory examinations revealed a severe degree of uremia, hyperphosphatemia, acidosis and anemia (table 2). The uremic state became more and more pronounced, she lost her appetite entirely, and vomited nearly all food. Bleeding from the nose and the intestinal tract appeared, and the girl died finally from uremia and anemia.



FIG. 5. Kidneys and pelvic organs, posterior aspect. The contraction of kidneys, hydropelvis and hydroureters are on view. Note the infantile configuration of the uterus.

Necropsy was performed two hours after death by Dr. E. Freund. Anatomical diagnosis: Hydropelvis and hydroureter, bilateral, of unknown origin. Marked atrophy of kidneys. Chronic interstitial nephritis. Focal suppurative (ascending?) nephritis.

Secondary hypertrophy of two parathyroid glands.

Foci of suppurative bronchopneumonia of the right lung.

Terminal verrucous thromboendocarditis of the mitral valve.

Osteoporosis of petrous bones.

Hypoplastic uterus and adnexes.

The body was that of a young female measuring 135 cm. in length. No secondary sex characteristics were present. The skin was pale. There were brown pigmented spots scattered over face, trunk and extremities. Emaciation was marked. There was no edema and no palpable lymph nodes.

The more important findings were as follows. Urinary tract (figure 5): The right kidney weighed 25 gm., and measured 5 by 2 by 2 cm. The organ was firm in



FIG. 6. Larynx with thyroid and parathyroid glands, posterior aspect (moderately enlarged). Two parathyroids are on view, the right one measuring in nature 20 by 8 by 5 mm.

texture. The thin fibrous capsule was firmly adherent to the cortical surface. Cut surface was yellowish-brown throughout. Cortico-medullary border was not clearly defined. The renal pelvis and calices were considerably dilated and the renal papillae were entirely flattened. Corresponding with the dilated calices the parenchyma was markedly atrophic; it measured in some areas but 2 mm. in thickness and in no place more than 20 mm. The right ureter was extremely dilated, measuring in its upper third about 10 mm. in diameter. Mucosa of pelvis and ureters was without defects. The left kidney weighed 30 gm., and measured 6 by 3 by 2 cm.; it was

similar in aspect to right kidney. The urinary bladder was moderately distended with urine. The mucosa was pale, with scattered verruca-like tiny elevations of reddish-brown color. Openings of ureters were without lesions.

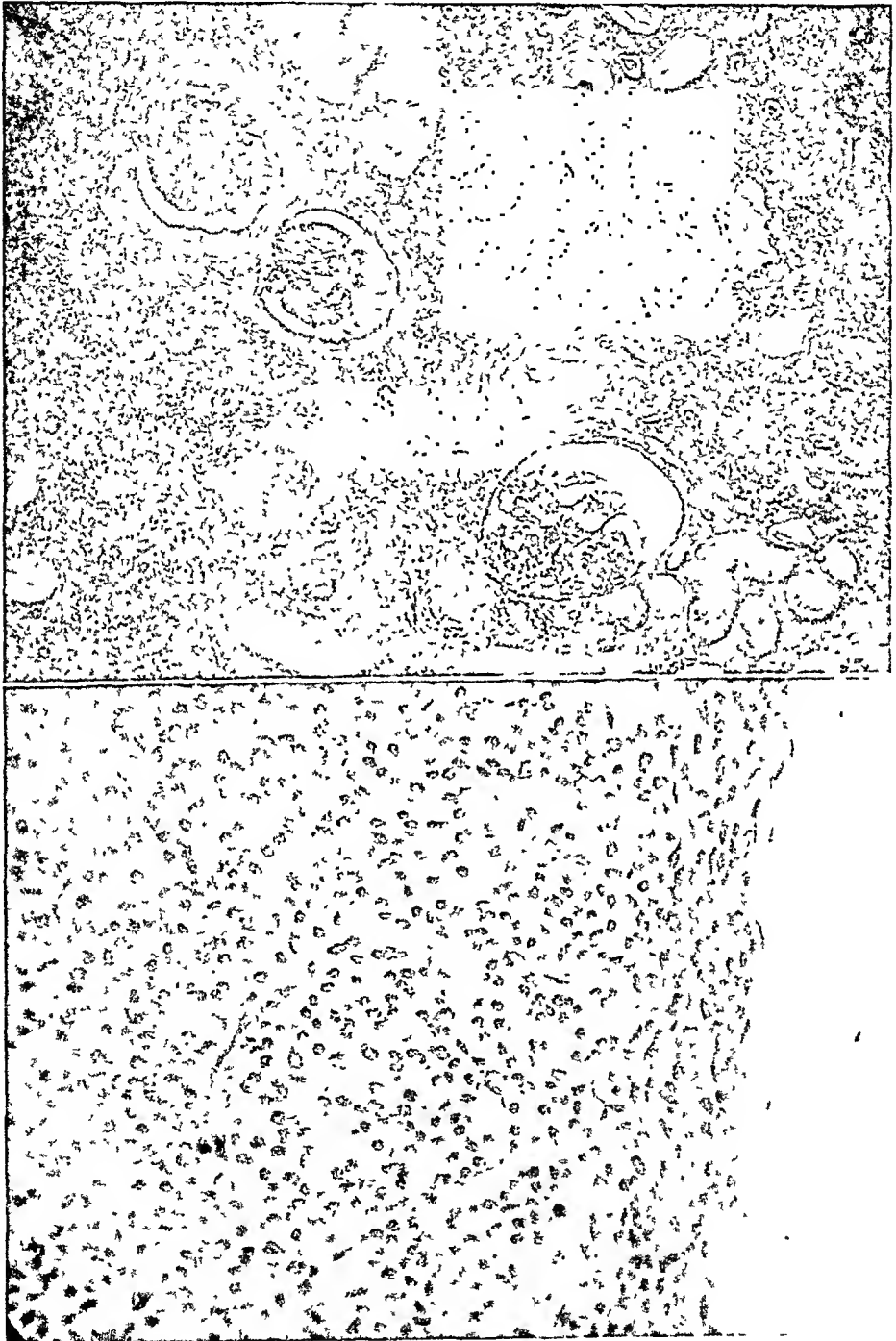


FIG. 7. (*Above.*) Section of the kidney (see text).

FIG. 8. (*Below.*) Section of the enlarged parathyroid gland (see text).



Parathyroid glands: In the place corresponding to the lower parathyroids, two round bodies were found, each one being about the size of a small bean (figure 6). Cut surface revealed yellowish-brown tissue, containing a dark reddish center.

Costochondral junctions were grossly without changes. Epiphyseal regions of long bones were not thickened. Calvarium could be sawed with ease.

Histological examination (Dr. H. Ungar). Kidneys: Glomeruli were irregularly distributed and diminished in number. In some instances they were larger than normal, with dilated spaces of Bowman, containing pale coagulated material (figure 7). Capillaries had normal content of nuclei.

There were also scattered glomeruli which were partially or entirely hyalinized. The degree of hyalinization varied in different areas, and was more marked in areas of extreme atrophy of the parenchyma.

Extensive atrophy of tubules was observed in the vicinity of all glomeruli. In irregular distribution there were groups of hypertrophic tubules, lined by clear cubical epithelium. The increased fibrotic interstitial tissue contained infiltrations of lymphocytes and scattered polymorphonuclear leukocytes and plasma cells. In one area a small abscess was found, surrounded by tubules distended with abundant cellular debris and leukocytes. The arterioles were without pathological changes; the medium-sized arteries showed marked thickening of all layers. There was only negligible increase of elastic fibers. The parathyroids were uniformly built of clear chief-cells. No cells of other types or fat-cells were found (figure 8).

## DISCUSSION

In its essential features our case fits well into the known picture of renal dwarfism and belongs to the group A(1) of Rule and Grollman (primary renal disease with well recognized anatomical changes). It presented stunted growth (without manifestations of rickets), infantilism, and severe impairment of the renal function, leading to uremia and death. Moreover, the autopsy revealed hypertrophy of the parathyroid glands of the type found in secondary hyperparathyroidism. The kidney lesions were those which are found in the majority of cases of renal dwarfism, i.e., bilateral congenital dilatation of the pelvis and the ureters with atrophy of the renal parenchyma and interstitial nephritis. Besides, there were signs of superimposed focal suppurative nephritis. Also, the age of the patient at the time of manifestation of severe renal symptoms and of death corresponds to that usually attained in such cases. The absence of fundus changes and of pronounced degrees of hypertension, as well as the mental alertness, are likewise common in this disorder.

There are, however, some points which seem worth stressing, as they may contribute to the solution of the question of the connection between the disturbed renal function and the skeletal changes.

In our case, the retardation of growth was noted as early as in the first year of life, and was already marked at the age of one and one-half years. It is highly improbable that already at this early date the kidney function was disturbed to such a degree as to be the cause of the impaired growth. On the other hand, the kidney lesion belonged to the congenital type of this disorder and was likewise present at the time of birth. It seems, therefore, justified to assume that in our case there existed a congenital malformation of the kidneys, together with a congenital tendency to dwarfism which became manifest as early as the first months of life.

A further proof for this assumption is to be found in the family history. The mother and the sister were definitely below normal height, and both these members of her family showed the same malformation of the right kidney as our patient had on both sides.

The roentgenological appearance of the right kidney is strikingly similar in all three cases, and this fact in itself deserves special stress, as it seems to be the only case on record in which three members of one family had the same congenital malformation of this type.

We may say, accordingly, that this case of renal dwarfism was caused primarily by a congenitally present kidney malformation and a hereditary tendency to stunted growth, both of these based on a familial trait, but most pronounced and leading to the fully developed picture of renal dwarfism only in our case. As to a common root of these disorders in a pituitary or diencephalic factor, we can make no definite statements, as other abnormalities usually connected with such a disturbance were lacking, but it may be mentioned that the lack of secondary sex characteristics and the hypoplasia of the uterus and its adnexes point in this direction.

For our case we can, therefore, dispense with any theory of chemical or functional interrelationship between the kidney disorder and the dwarfism, in order to explain the clinical and laboratory findings which were present until two to three months before her death. Up to this time blood urea and uric acid were elevated without pronounced hypocalcemia, hyperphosphatemia or severe acidosis, and it was only about two months before her death that the inorganic phosphorus in the blood began sharply to rise and to reach 13.8 mg. per cent, and the acidotic state to become severe and to depress the alkali reserve to 14.7 vol. per cent  $\text{CO}_2$ . It may be repeated here that the microscopic findings were those of an active interstitial nephritis and foci of suppuration within the renal parenchyma, and these alterations more than the primary congenital malformation caused the extreme reduction of normal tissue and the final breakdown of the kidney function, with the severe alterations in the blood chemistry, during the last two to three months (table 2).

As to the hypertrophy of the parathyroid glands which was found at autopsy, it may well be assumed that it resulted from the chemical changes brought about by the renal insufficiency during the last two to three months, a time interval which seems to be sufficient, according to the experiments of Pierre, de Boissezon and Lombard,<sup>54</sup> to bring about a marked increase in the weight of these glands. This hypertrophy, however, was apparently not present long enough to produce more than the slight osteoporosis which was observed in the petrous bones.

This interpretation of the course of events in our case is primarily in accordance with the theory of renal dwarfism as a syndrome of parallel, non-interdependent, congenital disturbances, affecting the general growth and development and the urinary tract. However, the hypertrophy of the parathyroid glands and the slight osteoporosis fit also into the other theory, maintaining a causal relationship between the kidney insufficiency and the skeletal deformities. Our case actually needs both of the described theories for a satisfactory explanation, the former for the manifestations during the greater part of the patient's life and the latter for the last few months after the kidney insufficiency had become extreme and had led to severe acidosis and phosphatemia. It seems possible that in other cases, too, there may be two stages in the development of the syndrome:

in the first, latent kidney damage and stunted growth, both of them congenital, are present; in the second manifest renal insufficiency, hyperparathyroidism and structural changes of the bones are observed. A careful correlation of all available data; especially regarding the time of onset of the various clinical symptoms and of the blood findings, is necessary in order to find out, in questionable cases, the presence of one, or possibly both of the above described mechanisms. In some cases, as in ours, examination of other members of the family may prove helpful, in order to establish proof of the congenital character of both conditions.

### SUMMARY

The syndrome of "renal dwarfism" may be explained by two different theories. The first, prevalent in the English and American literature, assumes a causal dependence of the bone changes upon the kidney disorder; the second, advanced chiefly by French and German authors, describes both groups of changes as parallel, non-interdependent, congenital malformations.

A case is described of renal dwarfism in a girl of 14 years, without bone deformities, but with hypertrophy of the parathyroid glands and slight osteoporosis. The congenital nature of the kidney disorder, the retardation of growth since early infancy, and the presence of corresponding kidney disorders and subnormal stature in two other female members of the same family seem to justify the explanation of this case on the basis of the theory of "multiple congenital malformations." The supervening secondary hypertrophy of the parathyroid glands and the slight osteoporosis are explained, on the basis of the other theory, as a result of the renal insufficiency.

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## THIOURACIL IN ACUTE THYROIDITIS \*

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ACUTE thyroiditis has been treated in a few instances with thiouracil<sup>1</sup> and the results have been very encouraging. The following two cases are reported to show the striking response to this drug after a thorough and adequate course of penicillin and sulfadiazine had failed to relieve any of the signs or symptoms.

### CASE REPORTS

*Case 1.* A female, married, age 38, was seen on September 1, 1945, with a history of frequent chills and fever occurring, especially at night, during the preceding 10 weeks. She complained of an aching feeling in the head, pain in the neck in the thyroid region which spread into the jaws and upward into the neck, palpitation, distress in the abdomen not related to any special food-taking, loose stools, anorexia, weakness, and loss of about 20 pounds in weight during the interval of the past 10 weeks. She claimed that her health was good prior to the onset of this trouble and that her menstrual history was normal. Her past history revealed a gall-bladder operation and an appendectomy nine years previously. She has three children, the youngest six months of age.

Examination showed an acutely ill individual with a temperature of 99.5° and an enlarged, smooth, hard, tender thyroid, especially the lower portion of the lobes on both sides. Her throat and mouth were negative, as were the heart and lungs. Her blood pressure was 120 mm. Hg systolic and 82 mm. diastolic. Her abdomen was negative and also her pelvic organs. There was no evidence of trouble in the extremities.

Her laboratory report showed a 52 per cent hemoglobin, 10,700 white cell count, and a 3,550,000 red cell count with a sedimentation rate of 102 mm. in an hour. The hematocrit was 26.25 per cent MCV 74, MCH 25, and MCHC 36, revealing a microcytic anemia. The common agglutination tests and blood culture were negative, and the Wassermann test was negative. The blood sugar reading was 88 mg. per cent, and the non-protein nitrogen was 38 mg. per cent. The urine examination was negative. The basal metabolism was plus 6 per cent. Roentgen-ray examination of the chest was negative.

Sulfadiazine in doses of 1 gm. every four hours for 10 days and again for six days after an interval of one week gave no signs of improvement. Penicillin in doses of 30,000 units every three hours intramuscularly for six days also failed to show any changes in the signs and symptoms.

Thiouracil (Deracil) † in doses of 0.2 gm. three times daily was started on Sep-

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† Deracil used in case 1 was supplied by Lederle Laboratories.

tember 18, 1945. Her temperature became normal in 48 hours and remained so from that time on, with an immediate improvement in all her symptoms. The gland remained swollen and hard, but this too gradually subsided, so that on February 15, 1946, no evidence of swelling could be found.

Thiouracil was given in full dosage of 0.2 gm. three times daily for one week; then the same dose twice daily for two weeks; and then 0.1 gm. daily for three months.

Six weeks after discontinuing the drug there was a slight recurrence of the acute symptoms with slight swelling of the lower portion of both lobes. Thiouracil in doses of 0.2 gm. three times daily for one week and twice daily for another week caused all signs and symptoms to disappear, and there has been no evidence of recurrence since that time. She has gained weight, her blood picture has become normal, she is working and apparently has no residual effects from this inflammatory condition.

*Case 2.* A male, age 32, was seen on September 10, 1946, with a complaint of chills and fever and sweats at night extending over a period of three weeks, during which time he lost weight, became weak, was unable to eat, and had pains in his neck extending up toward the ears. He had headaches and had pains in his arms and legs, especially at night. His past history showed no evidences of this condition prior to the onset above noted. While in the South Pacific he had been ill for one month with jaundice and had, for several months prior to his discharge from the Army, complained of pain in his ears, the cause of which could not be determined. His family history was negative.

Examination showed an acutely ill individual with a temperature of 99.6°, a pulse of 90, and a hard, tender swelling of the lower poles of both lobes of the thyroid, a negative chest, and a blood pressure of 120/82. His liver and spleen were not enlarged, and there was no tenderness in the abdomen. His extremities were negative. Laboratory examination showed 80 per cent hemoglobin, 14,700 white blood cells, and 4,370,000 red blood cells, with a sedimentation rate of 33 mm. in one hour. The common agglutination tests, Wassermann test, and blood cultures were negative. Basal metabolic rate was plus 9 per cent. His blood sugar was 114 mg. per cent and the non-protein nitrogen 32 mg. per cent. The blood smears were negative for malaria, and his icterus index was 11.3. His urine examination was negative. He was hospitalized on September 10 and placed on 30,000 units of penicillin every three hours for six days with no material change in his condition or his complaints. His temperature during this time rose to spikes of 101°, and his pulse varied from 72 to 104. On September 16 he was given 0.2 gm. of thiouracil three times a day, and this was continued for seven days, when the dose was reduced to 0.2 gm. twice daily and continued as such until November 1.

The results of this treatment were a normal temperature 24 hours after beginning administration of the drug, with no subsequent elevation, and a gradual diminution of all symptoms and findings started immediately. His white blood count was 6,500 five days after beginning use of the drug. On November 1, there was no longer any evidence of swelling of the gland, no chills or fever or pain, and he has remained perfectly well since that time. He has regained his normal weight, has been working at a strenuous occupation, and on several instances has been examined with no evidence of any residual findings.

#### COMMENT

The pharmacological reason for this improvement is difficult to understand, but the response in both cases was so prompt and similar that it could not be a coincidence. The therapeutic results indicate that the infection probably, in some way, is linked up with the process of the production or liberation of thyroxin.

The failure of both penicillin and sulfadiazine to improve the first case and the lack of effect from penicillin in the second case are especially noted.

Probably the swelling of the gland in the first case would have disappeared in a shorter time if the dosage of 0.2 gm. twice daily had been continued a few weeks longer, and the recurrence of the symptoms thereby might have been avoided.

### CONCLUSIONS

Two cases of acute thyroiditis responded rapidly to treatment with thiouracil.

These two cases were resistant to treatment with other methods, including penicillin and sulfadiazine.

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### ANTERIOR PITUITARY INSUFFICIENCY (PANHYPOPITUITARISM—SIMMONDS' DISEASE), PITUITARY MYXEDEMA AND CONGESTIVE HEART FAILURE (MYXEDEMA HEART); REPORT OF CASE AND FINDINGS AT NECROPSY \*

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ANTERIOR pituitary insufficiency (panhypopituitarism) may result from any pathologic process that destroys the anterior lobe. The most common lesion is the chromophobe tumor. Less frequently, other nonfunctioning neoplastic lesions, granulomas, chronic infections, atrophy, necrosis, hemorrhage, infarction or miscellaneous vascular disturbances account for pituitary failure. The terms "Simmonds' disease" and "Simmonds' cachexia"<sup>1</sup> have been applied, often indiscriminately, either to pituitary necrosis that occurs postpartum or to cachectic patients having, or thought to have, anterior pituitary insufficiency for other reasons. Clinically, the symptom complex that characterizes postpartum pituitary necrosis is essentially the same as that which occurs in conjunction with any other destructive lesion of the anterior lobe of comparable magnitude. Sheehan<sup>2</sup> has pointed out that cachexia, as a symptom of postpartum pituitary necrosis, is the exception rather than the rule. The same dictum applies for that matter to any other form of anterior pituitary insufficiency. Even when cachexia occurs, as it undoubtedly does in some instances, there is considerable reason to suspect that it may have very little or nothing to do with the anterior pituitary insufficiency per se but that it results from the same factors that cause cachexia in other patients; namely, an inadequate caloric intake or vomiting or both. Regardless of its interpretation, the fact remains that in a group of patients having severe anterior pituitary insufficiency of comparable degree, some are fat, some are nor-

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† Deceased.

mal in weight, others are lean and a few are cachectic. The hypotheses that can be, and have been, offered to explain this paradox leave much to be desired and for present purposes, can be disregarded without comment.

The emphasis that has been placed on cachexia as a sign of postpartum pituitary necrosis has had unfortunate diagnostic consequences. In many instances, because of the presence of cachexia, anorexia nervosa has been diagnosed erroneously as Simmonds' disease and conversely cases of frank postpartum pituitary necrosis have been overlooked because the patient was not cachectic. There is, therefore, little excuse for retaining the terms "Simmonds' disease" or "Simmonds' cachexia." Clarity of thought would be greatly facilitated if the gross pathologic and physiologic status of the patient were expressed more specifically, as for example "postpartum pituitary necrosis with anterior pituitary insufficiency, with (or without) cachexia" or "chromophobe tumor of the pituitary body with anterior pituitary insufficiency and pituitary myxedema with (or without) cachexia" and so forth.

The signs and symptoms of severe anterior pituitary insufficiency are to a large extent, but probably not entirely, the result of varying degrees of secondary gonadal, adrenal and thyroid insufficiency. Generally they are sufficiently distinctive to enable one to differentiate it from other endocrinopathies. Often the diagnosis is evident on inspection by the characteristic waxy pallor, feebly growing beard and sparse cutaneous, pubic and axillary hair. The skin is soft and fine. In women the uterus is small and the vaginal mucosa is hypoplastic; in men the testes are soft or atrophic. When the disease antedates puberty, sexual development ceases. Skeletal growth likewise usually stops, but if it should continue, as it does occasionally, the extremities become unduly long and the habitus of the patient resembles that of the eunuch. Such cases, however, are the exception rather than the rule and the consequence of this fact is that a eunuchoid habitus is usually indicative of a primary gonadal disorder rather than anterior pituitary insufficiency. As has been mentioned, the patient may be fat, thin or of normal weight but the distribution of fat may be feminine in character. Frequently the patient complains of weakness. There is a history of decreased or absent potentia, anaphrodisia or amenorrhea without hot flushes. Laboratory examinations show a low basal metabolic rate, a flat glucose tolerance curve, normal blood or varying degrees of anemia, a "positive water test" such as occurs in Addison's disease and decreased or absent urinary 17-ketosteroids and gonadotropins. Depending on the nature of the pathologic process and the amount of residual functioning pituitary tissue that has escaped destruction, some of these symptoms and signs may be absent. For example, in cases of chromophobe tumor, amenorrhea may be for years the only symptom of the disease. Even in cases of severe anterior pituitary insufficiency the function of gonads, thyroid and adrenal glands may not be disturbed equally in any particular patient. For example, in a few cases adrenal cortical insufficiency is so prominent that the clinical picture presented by the patient greatly resembles that of Addison's disease, whereas in others adrenal cortical function is apparently so slightly affected that its insufficiency cannot be demonstrated with certainty. To a lesser extent the same is true of thyroid function. On the other hand, gonadal function is relatively easily upset by anterior pituitary failure and consequently in practically every instance evidence of gonadal failure can be obtained.

Ordinarily the clinical picture just described bears little resemblance to pri-



primary myxedema and, conversely, the ordinary case of spontaneous or postoperative myxedema does not simulate anterior pituitary insufficiency. Occasionally, however, during the course of anterior pituitary insufficiency, the patient acquires secondary myxedema, presumably because of inadequate production of thyrotropic hormone by the anterior pituitary body. When this occurs, the skin becomes thick, dry, coarse and scaly and nonpitting edema of the hands, face and lower extremities appears. This secondary myxedema resembles ordinary myxedema in every major or minor respect. In fact, it is myxedema but a myxedema superimposed on the original clinical picture of anterior pituitary insufficiency. Means, Hertz and Lerman<sup>3</sup> suggested that the term "pituitary myxedema" be applied to this condition so as to distinguish it from ordinary or primary myxedema. Although one might question the merits of this particular term, there are good reasons for making the distinction. All of the symptoms of primary myxedema respond to treatment with desiccated thyroid and the patient is "cured" as long as he continues to take the medication. Pituitary myxedema likewise responds to administration of desiccated thyroid but the patient remains ill because of the other disorders attending anterior pituitary insufficiency, which naturally are not corrected by desiccated thyroid. Furthermore, some patients who have pituitary myxedema may become very ill and die when first treated with desiccated thyroid, possibly because of the precipitation of acute adrenal cortical insufficiency.

If the patient has the signs and symptoms of an expanding intrasellar tumor such as bitemporal headache, bitemporal hemianopsia or other characteristic changes in the perimetric fields and characteristic roentgenologic changes in the sella turcica, it is relatively easy to make a correct diagnosis. If the patient is a woman and her illness began after a difficult delivery, complicated by shock hemorrhage or both, one can suspect that she has had "pituitary apoplexy" and that her illness is the consequence of the resulting pituitary necrosis. On the other hand, if there is no evidence of a pituitary tumor and if the condition did not develop post partum, the myxedema may dominate the clinical picture to such an extent that the signs and symptoms of the primary pituitary insufficiency are overshadowed and consequently not detected. In such cases recognition of pituitary myxedema may be very difficult.

Primary myxedema may lead to characteristic and almost pathognomonic changes in the status of the heart. Zondek,<sup>4</sup> Assmann,<sup>5</sup> Meissner,<sup>6</sup> and Fahr<sup>7</sup> were among the first to demonstrate this fact. Subsequently their observations have been confirmed repeatedly by others. The "myxedema heart," or, as Means<sup>8</sup> prefers, "the heart in myxedema," is characterized by flabby musculature and enlargement of all four chambers, probably because of dilatation. The minute volume output is reduced. In the electrocardiogram, the complexes are of low amplitude, the T-waves, particularly in Leads I and II, are flattened or inverted and other less significant abnormalities may be present.\* In our experience, as well as that of Means,<sup>9</sup> gross congestive heart failure rarely occurs, probably because, as Means pointed out, with "reduction in the heart's capacity for work there goes a parallel reduction in the amount it is called upon to perform." On the other hand, cases reported by Fahr, by Mussio Fournier,<sup>10</sup> and by La Due<sup>11</sup> leave little room for doubt that in certain instances primary myx-

\* Mussio Fournier and his associates have recently published an excellent monograph on the cardiovascular apparatus in thyroid insufficiency.

edema may be accompanied by all signs and symptoms of severe congestive heart failure and that the myxedema is largely, if not entirely, responsible for the occurrence of these signs and symptoms.

In this connection the case of La Due is of considerable importance. The patient was a woman, aged 55 years. She had myxedema and the signs and symptoms of congestive heart failure. Arteriosclerotic damage of the myocardium was conspicuously lacking and the coronary arteries were perfectly normal except for one small atheromatous nodule, which reduced the caliber of one of the small branches of the left descending coronary artery to a half. La Due also pointed out the interesting similarity of the myocardial lesions to those found in beriberi heart. In addition, he reviewed the history of another patient who had myxedematous heart, who did not respond to intensive thiamine and vitamin B complex therapy for 33 days. There was, however, a rather rapid response to treatment with desiccated thyroid within eight days and, after 25 days of treatment, the electrocardiogram was essentially normal.

La Due's observations seem to establish the fact that the cardiac pathologic physiologic state of patients having myxedema results from thyroid deficiency rather than thiamine deficiency. They do not preclude the possibility that utilization of available thiamine by the myocardium might be impaired by inadequate thyroid function.

The foregoing remarks regarding the heart apply to cases of primary myxedema. That they may be applicable to cases of pituitary myxedema is suggested by the case reported by Darley, Gordon and Neuburger<sup>12</sup> and by the observations made on the patient the report of whose case follows. In the former case, issues are somewhat confused by the presence of "an old rheumatic mitral valvulitis." In our case the valves and the coronary arteries were normal.

#### CASE REPORT

The patient was a white man, aged 47 years, who came to the Mayo Clinic February 16, 1943, because of weakness, anorexia and dyspnea on exertion. On the whole his health had been good until the onset of his present illness, which he thought dated back to 1939 or 1940. In 1931 he had sustained an injury to the left eye from a glancing dull object. There was no loss of consciousness or headache but the left eye became swollen, red and painful for several days without any known residual. In 1936, following a cold in the head, his left eye became swollen to twice its normal size, reddened and painful. There was transient impairment of the sight. Following treatment the swelling receded entirely, but slight strabismus and ptosis persisted.

At no time was the patient known to have hypertension. In 1939 his physician commented on the redness of his cheeks and thought that he might have high blood pressure. However, the blood pressure was found to be normal (130 mm. of mercury, systolic). There was no history of rheumatic fever.

The onset of the patient's present illness was insidious. Other than a gradual decrease in libido for the preceding three years, he had not noticed any change until February, 1942, when he became progressively weaker. His appetite declined and he lost weight. The weakness was most pronounced toward the end of the day and it became so severe that he had to be helped into his car after office hours. At the onset of his illness he weighed 169 pounds (76.7 kg.) but five months later he weighed 129 pounds (58.5 kg.).

In the latter part of May, 1942, the patient became so weak that he could hardly sit at his desk. Associated with the weakness was mild exertional dyspnea. By this

time he had complete absence of libido and potentia. He consulted his physician, who prescribed rest in bed and general therapeutic measures. As improvement did not result, he entered a hospital on June 15, 1942. There he was found to have a low basal metabolic rate, low blood pressure, and mild anemia. A presumptive diagnosis of Addison's disease was made. Within three weeks he improved rapidly following the administration of thiamine chloride and injections of suprarenal cortical extract. His strength and appetite returned and his weight increased to 174 pounds (78.9 kg.). He was permitted to leave the hospital July 6, 1942. His family physician was advised to administer daily injections of suprarenal cortical extract (5 c.c.) for two weeks and then bi-weekly injections for three weeks.

Progress continued until August, 1942, when he stopped taking the injections of suprarenal extract because of nervousness. In November, 1942, he had a return of weakness and anorexia, whereupon he took three injections of suprarenal cortical extract and again his condition improved. This time the improvement did not persist and soon his weakness and dyspnea returned. In January, 1943, he contracted a severe head cold and became very ill. This illness was characterized by weakness, anorexia, dyspnea, orthopnea with nocturnal paroxysms, enlargement of the abdomen (ascites?), and cough productive of frothy sputum. He had no noticeable edema of the ankles. In addition he had mild diarrhea of soft watery stools, two to three times daily. On questioning, he stated that he had always had rather sparse beard and body hair and had noticed no decrease; however, the texture of the hair of the scalp had become silky. He had also noticed that the skin had taken on a yellowish hue and had become dry. He had noticed no abnormal sensitivity to cold.

*Examination.* The temperature, pulse and respirations were essentially normal. The blood pressure in millimeters of mercury was 94 systolic, 68 diastolic. The height was 177 cm., and the weight 76.7 kg. There was no evidence of loss of weight; on the contrary he was well developed and well nourished. His general appearance immediately suggested the diagnosis of myxedema to the physician who first examined him. He looked older than his stated age. There was fine wrinkling of the skin, which was thin, dry, scaly and pale yellow. The hair was very soft and silky in texture. The beard was very scant and there was no axillary hair. Less than normal pubic hair was present and its contour was feminine in type.

The head was not remarkable except for the left eye. There was incomplete paresis of the left third and fourth cranial nerves. The left pupil was almost fixed and there was marked limitation of upward and downward movements with only slight limitation of inward rotation. There was weakness of the left orbicularis oculi muscles. The visual fields were normal. Nothing of consequence was seen in the ocular fundi.

There was no glandular enlargement. No thyroid tissue was palpable in the neck.

There were bilateral hydrothorax and pulmonary congestion. The heart was markedly enlarged both to the right and to the left. There were numerous extrasystoles and the sounds were very distant. No apical impulse was seen or felt.

The abdomen was enlarged. There was ascites and the liver was tender and palpable 2 inches (5 cm.) below the costal margin. The spleen was not felt. The genitalia appeared normal. The testicles and prostate felt normal in size and consistency. The recovery phase of the ankle jerks was slow and typical of those seen in cases of myxedema.

Laboratory findings are recorded in table 1.

*Diagnosis.* That the patient had severe anterior pituitary insufficiency (post-traumatic?) and congestive heart failure was easily recognized. It was also evident that the hypopituitarism was associated with secondary gonadal and thyroid insufficiency. By inference it seemed likely that adrenal cortical function was also impaired and the likelihood was strengthened by the advent of such unfavorable clinical symptoms as hiccup, nausea, abdominal pain and decreasing blood pressure when the

## TABLE I

### Laboratory Findings

Urinalysis		
Specific gravity	1.024	
Reaction	Acid	
Albumin	Grade 1*	
Sugar	0	
Hematologic findings		
Hemoglobin	10.8 gm. per 100 c.c. blood	
Erythrocytes	4,010,000 per cu. mm. blood	
Leukocytes	5,400 per cu. mm. blood	
Comment on blood smears	Increased erythrocyte regeneration with mild hypochromasia	
Blood chemical findings		
Urea	34 mg. per 100 c.c. blood	
Sugar	94 mg. per 100 c.c. blood	
Chloride (as NaCl)	561 mg. per 100 c.c. plasma	
Sodium	308 mg. per 100 c.c. plasma	
Potassium	20.6 mg. per 100 c.c. plasma	
Protein	6.5 gm. per 100 c.c. serum	
Cholesterol	157 mg. per 100 c.c. plasma	
Carbon dioxide	42.8 vol. per cent	
Bilirubin, direct	0	
indirect	0.75 mg. per 100 c.c. serum	
Miscellaneous		
Water test†		
Procedure I: $\frac{\text{greatest vol. day urine}}{\text{vol. of night urine}}$	0.14	
Procedure II: A (urea-chloride index)	12	
Glucose tolerance test	Blood sugar, mg. per 100 c.c.	Urine sugar
Fasting	81	0
½ hour	119	0
2 hours	144	0
3 hours	140	0
Basal metabolic rate	-23 per cent	
Prolan (gonadotropic)	Less than 10 rat units per liter	
Total 17-ketosteroids	0.4 mg. per 24 hours	
Liver function	Dye retention, grade 2*	
Venous pressure	21.4 mm.	
Circulation time (arm to tongue)	15 sec.	
(arm to lung)	6 sec.	
Flocculation test for syphilis	Negative	
Roentgenograms		
Head	Calcified petroclinoid ligament. Rather marked calcification left internal carotid artery	
Thorax	Cardiac enlargement. Some exaggeration hilar marks on both sides, probably due to passive congestion. Extensive thickening of pleura and possibly fluid on right. Some compression basal portion right lung	
Electrocardiogram	Rate 100; sinus tachycardia with ventricular premature contractions; notched QRS I and III, slurred II, very low amplitude QRS I, II, III, diphasic I and III, slight left axis deviation (PR = 0.20 second). IV-R: Positive T. Low amplitude QRS Cr -2. Low amplitude. Positive T. Slightly elevated ST segment	

\* On the basis of 1 to 4, in which 1 represents the mildest and 4 the most severe condition.

† Procedure of Robinson, Power and Kepler.

intake of sodium chloride was restricted as a therapeutic measure to restore cardiac compensation. Furthermore, these symptoms were relieved by intramuscular administration of 10.0 c.c. of cortical extract.

The cause of the heart failure was the most difficult diagnostic problem. Here five possibilities had to be considered.

1. Preexisting hypertensive heart disease. This possibility seemed to be excluded fairly well by the clinical history, the electrocardiogram and the shape of the roentgenologic silhouette of the heart.

2. Pericarditis with massive effusion. This possibility seemed unlikely because of the absence of the usual etiologic factors responsible for this condition. In addition the physical signs which often accompany massive pericardial effusion were absent and the venous blood pressure was not increased.

3. Beriberi heart. This possibility was suggested by the shape of the heart shadow, the electrocardiogram and the low venous pressure. As a possibility it was

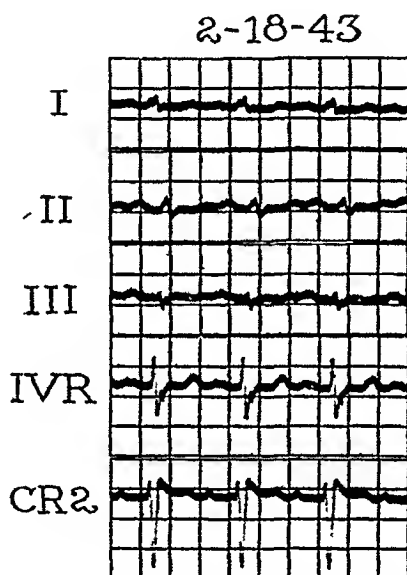


FIG. 1. Electrocardiogram of the patient.

never very satisfying. None of the other physical signs or symptoms of beriberi were present, there was no history of dietary inadequacy and the intravenous administration of 40 mg. of thiamine daily did not produce either subjective or objective improvement.

4. Hemochromatosis was considered very seriously in the diagnosis. It could account for the appearance of pituitary insufficiency, the enlarged liver and the congestive heart failure. The patient was only slightly pigmented but in cases of hemochromatosis dense pigmentation need not be present. This diagnostic possibility was abandoned when biopsy of the skin failed to show characteristic deposits of iron.

5. "Myxedema heart." This possibility had much to recommend it. The low venous pressure, the pattern of the electrocardiogram (figure 1) and the shape of the enlarged heart were consistent, the patient clinically appeared to have myxedema and the basal metabolic rate was low ( $-23$  per cent) even though he had congestive heart

failure. Nevertheless, in spite of this evidence, we were reluctant to make an unqualified diagnosis of this for several reasons. The degree of myxedema was mild when compared with the severity of the heart failure. Furthermore, primary myxedema is rarely accompanied by nocturnal dyspnea and severe, rapidly progressive heart failure and whether or not myxedema secondary to hypopituitarism could ever lead to congestive heart failure was certainly a question without answer in the literature. After weighing the pros and cons we finally concluded that a diagnosis of "myxedema heart" was the most likely of the various possibilities which we had considered.

*Treatment and Course.* While the patient was being examined in the hospital, his heart began to fail rapidly and relief of the distressing symptoms attending the congestive heart failure required first attention. It was hoped that this could be accomplished by nonspecific measures and that subsequently specific treatment for the adrenal cortical and thyroid insufficiency could be instituted.



FIG. 2. Dilatation of left ventricle. Weight: 507 gm.

The treatment employed did not work out satisfactorily. As mentioned elsewhere, restriction of sodium chloride precipitated symptoms suggesting adrenal cortical insufficiency. These symptoms responded to the administration of 10.0 c.c. of adrenal cortical extract and the unrestricted use of table salt. Simultaneously, however, the patient became more dyspneic and edematous. Solutions of hypertonic glucose and aminophylline gave some relief, but the patient remained critically ill. One cubic centimeter of salyrgan was then given intravenously. Diuresis was prompt and copious and the patient improved subjectively and objectively. However, improvement was transient. There developed marked dyspnea and an irregular tachycardia suggesting paroxysmal auricular fibrillation. He was placed at once in an



FIG. 3. Atrophy of pituitary body, above on left. Normal pituitary body for comparison, upper right. Atrophy of adrenal glands (middle) compared with normal adrenal glands below.

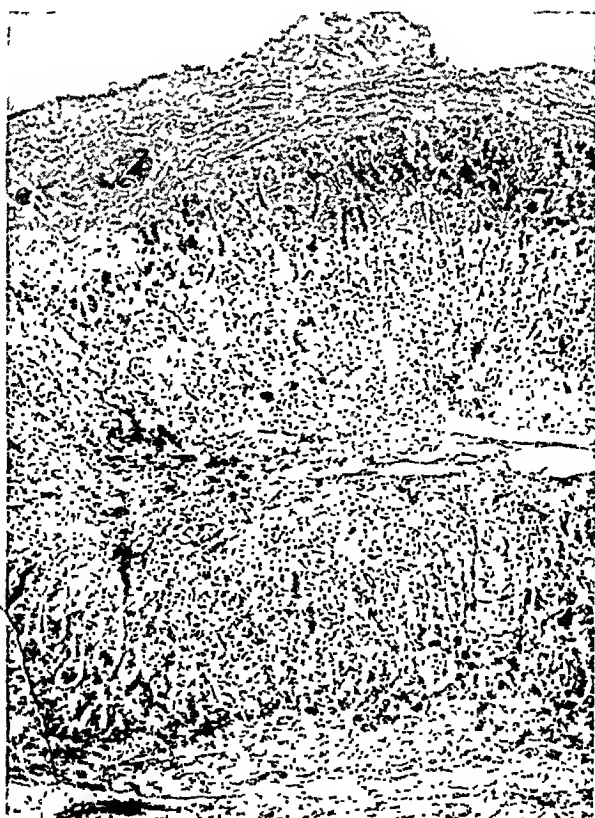


FIG. 4. Atrophy of adrenal cortex ( $\times 55$ ).

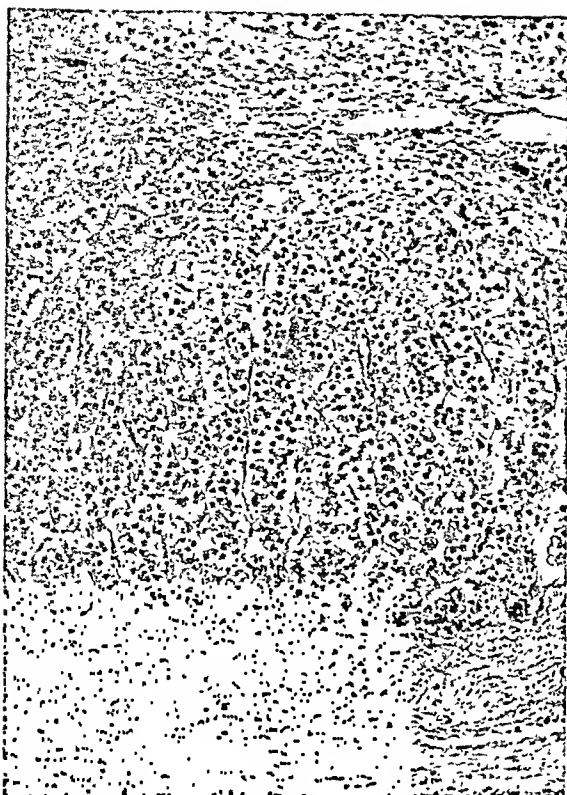


FIG. 5. High-power view of adrenal cortex. Medulla not shown ( $\times 115$ ).

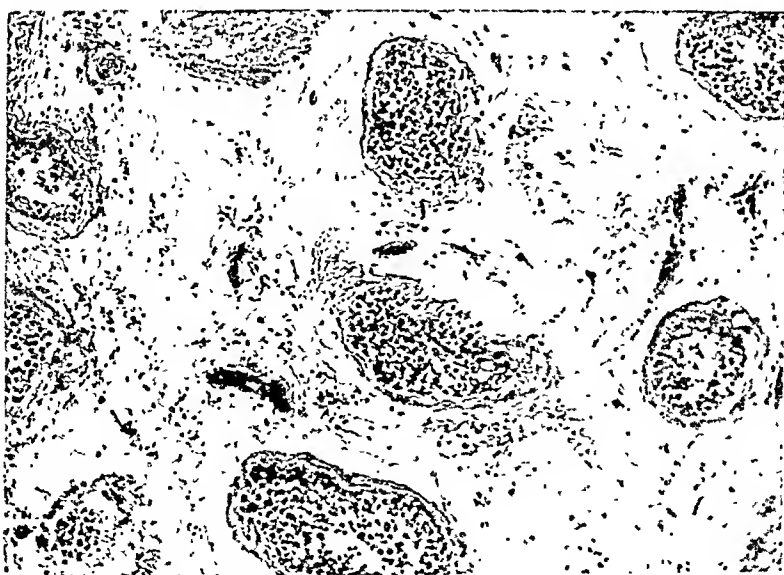


FIG. 6. Atrophy of testis ( $\times 85$ ).





FIG. 7. Atrophy of thyroid (right). Normal thyroid gland for comparison (left).

oxygen tent and was given 6 c.c. of cedilanid intravenously. Cardiac rate and rhythm became normal and the patient felt better. Four hours later, he was given another 6 c.c. of cedilanid intravenously. Shortly thereafter, he vomited and while doing so he died, 13 days after admission to the hospital.



FIG. 8. Atrophy of thyroid with fibrosis and lymphocytic infiltration ( $\times 85$ ).

*Necropsy Findings.* The body measured 177 cm. in length and weighed approximately 180 pounds (81.6 kg.). There was no emaciation. The parchment-like skin was tinged with yellow. The hair on the thorax and the pubic region was fine and scanty.

Bilateral hydrothorax was present (right 1,000 c.c., left 200 c.c.) associated with hydropericardium (75 c.c.) and ascites (2,000 c.c.). No thymic tissue was found. The heart (figure 2) weighed 507 gm. as compared with a normal weight of 320 gm. computed on the basis of body weight and sex. The hypertrophy was most marked in the left ventricle. Both ventricles were greatly dilated. The myocardium showed interstitial fibrosis with vacuolar degeneration of some muscle fibers. There was no arteriosclerosis of the coronary vessels. The lungs showed a moderate degree of chronic passive congestion and small focal regions of organized pneumonia. Passive congestion was noted in the spleen.



FIG. 9. Cross section of pituitary, marked atrophy ( $\times 8$ ).

The pancreas was atrophic and there was interstitial fibrosis with slight fatty replacement of the acinar elements. The islands of Langerhans appeared normal.

The liver showed the typical picture of chronic passive congestion with early central necrosis associated with atrophy (1,398 gm.; normal 1,800 gm.).

The gastrointestinal tract was normal.

The two adrenal glands (figure 3) weighed only 5 gm. The medulla showed a relative increase as compared with the cortex. The cortical cells (figures 4 and 5) contained an abundance of lipoid and appeared to be histologically normal except for a marked decrease in thickness of the cortex due to a diminished number of cortical cells in the zona fasciculata. The zona glomerulosa was prominent. A few microscopic cortical adenomas were present.

The kidneys were normal except for a calcified cortical adenoma with psammoma bodies.

The prostate was normal in size and shape. Chronic interstitial prostatitis, grade 1 (on the basis of 1 to 4, in which 1 represents the mildest and 4 the most severe condition), was present.

The testicles (figure 6) were moderately atrophic. The spermatogenic tubules were small and showed marked decrease in spermatogenesis. The interstitial connective tissue was increased. The tubules were surrounded by a dense ring of hyaline connective tissue. There was a paucity of interstitial cells; occasional cells were seen and they showed degenerative changes.



FIG. 10. Atrophy and fibrosis of the anterior pituitary body. Lymphocytes in connective tissue ( $\times 85$ ).

The thyroid (figures 7 and 8) was atrophic and fibrous. It weighed 5 gm. and was of normal contour. The acini was small with normal-appearing colloid. There was a slight increase in lymphocytes present. In some regions a large percentage of acini had been compressed by increased fibrous connective tissue.

The sella turcica appeared normal. The pituitary body (figures 3 and 9) was flattened and atrophic. It measured 9 by 6 by 2 mm. The stalk was prominent. On inspection with a hand lens, the normal divisions of the pituitary were absent. To the left of the pituitary and continuous with it was a soft, cystic, yellow mass 5 mm. in diameter containing coagulated serum. A narrow rim of pituitary cells persisted and was compressed into a fusiform mass measuring 0.5 by 1 by 2 mm. A few eosinophilic, basophilic and chromophobe cells (figure 10) were demonstrated

in the mass by means of Mallory-Heidenhain stain. The replacing fibrous connective tissue contained a few lymphocytes.

The thoracic portion of the spinal cord showed a mild degree of hydromyelocele.

### COMMENT AND SUMMARY

In a case of severe anterior pituitary insufficiency resulting from pituitary atrophy the cause of the pituitary atrophy was not evident; it may have occurred as the result of trauma. The patient weighed less than he did when he was in good health but in no sense of the word was he emaciated or cachectic.

The basal metabolic rate was low and the patient's appearance suggested myxedema. Death resulted from congestive heart failure. The antemortem and postmortem status of the heart was consistent with the diagnosis of myxedema heart. No other cause of heart failure could be demonstrated at necropsy. The coronary arteries and the valves of the heart were normal.

At necropsy the pituitary body, thyroid gland, adrenal cortices and testes were atrophic.

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## EDITORIAL

### *SOME SPECIFIC ANTIMALARIAL DRUGS*

ALTHOUGH the drugs which have been in general use are, in most cases, potent in terminating acute attacks of malaria, there are important limitations to their effectiveness and some untoward results attending their administration. Even before the War attempts had been initiated to find more satisfactory specifics. With the advent of the War, the necessity of maintaining armed forces in areas in which malaria is highly endemic as well as the loss of the Dutch East Indies, the only source of quinine in significant quantities, made the problem urgent and acute. Systematic attempts to produce and test new preparations were carried out intensively, both in Great Britain and the United States. Reports of much of the work done in this country have been collected and recently published in a supplementary number of the *Journal of Clinical Investigation* (May, 1948).

The effect of the antimalarial drugs varies with the different species of malarial parasites and with different strains of the same species. It also differs in the various phases of the life cycle of the parasites and with their location in the body.

When sporozoites are inoculated by the bite of infected mosquitoes, they can be demonstrated in the tissues at the site of the bite and also in the blood provided large amounts are withdrawn within about 20 minutes and transfused into a susceptible subject. They very quickly disappear from the blood, however, and cannot again be so demonstrated until about the eighth day after inoculation (James, Boyd, Fairley). (As a rule they cannot be demonstrated in thick films until two to four days later.) There is still no direct evidence regarding this phase of the life cycle in man. Since the parasites must be undergoing development and multiplication somewhere during this period and since they cannot be demonstrated in the blood, presumably they must be in the tissues. In several species of avian malaria they have been demonstrated in the tissues within endothelial cells in the bone marrow, spleen, brain and other organs. There is a strong presumption (only) that this tissue, or exoerythrocytic, phase also occurs in human and other mammalian malaria. In any event this phase seems to be an essential part of the life cycle. It cannot be materially shortened, even by massive inoculation of sporozoites. How long this tissue phase persists is also not known. There is some presumptive evidence that its duration is protracted and that it is the source of the parasites which cause the repeated relapses, particularly characteristic of quartan and vivax infections.

An ideal drug or combination of drugs for the therapeutic control of malaria should be nontoxic in effective doses and should accomplish the following objectives. (1) It should promptly terminate individual attacks of fever and eliminate the parasites from the blood (asexual cycle), effecting

a temporary cure. (2) It should eliminate the parasites in the tissue phase also, thus preventing relapses and effecting a permanent cure. (3) Used as a prophylactic, in small daily or weekly doses, it should destroy the sporozoites or the organisms in the tissue phase, completely protecting the individual from infection; or, failing this, at least so inhibit their growth that clinical illness does not develop (suppressive effect). (4) It should destroy or devitalize the gametocytes and prevent infection of the mosquito vectors.

A temporary cure in this sense can be accomplished by a number of different drugs. Quinine does this satisfactorily in most cases of infection with all the species affecting man, and it is effective in doses which are not significantly toxic for the great majority of individuals, although minor but often annoying manifestations of cinchonism are common. The value of cinchona and its alkaloids in the treatment of malaria has been demonstrated by about three centuries of experience; and the fact that more potent drugs have been discovered does not lessen its effectiveness or necessarily imply that it has become useless.

Quinine, given prophylactically, is effective as a suppressive agent, but it does not prevent infection. It will cure permanently a significant proportion of cases of falciparum malaria, but it has little effect in preventing relapses in quartan or vivax infections after its administration is stopped. After a varying number of relapses, to be sure, the infection eventually dies out, but the development of an active immunity by the host undoubtedly plays an important part in the cure. This immunity, however, is only temporary, and it is limited to the species and largely to the particular strain of the species involved. Its value in preventing reinfection under natural conditions, therefore, is extremely limited.

The first important addition to the antimalarials (in 1924) was plasmochin (plasmoquine), now commonly termed pamaquine. Although this drug proved too toxic for general use, it showed some significant advantages over quinine. It killed or devitalized the gametocytes (crescents) of falciparum malaria. Although less effective than quinine in controlling an acute attack of malaria, Sinton et al.<sup>1</sup> (1928, 1930) showed that if pamaquine is administered simultaneously with quinine, a synergistic effect was obtained and a permanent cure was effected in many cases of relapsing vivax malaria. Their case material consisted of European soldiers in India, who were suffering from repeated relapses which had not been controlled by quinine alone. Of 64 cases receiving both drugs and observed for eight weeks following treatment, three relapsed, whereas of 38 controls receiving quinine alone, 15 relapsed within this period. Sinton's observations have been confirmed by a number of other observers working with similar case material; e.g., by Piebenga (1930) in Holland; by Manifold (1931) in British-Indian troops; by Thompson and Williams (1945) in British troops in the Medi-

<sup>1</sup> SINTON, J. A., SMITH, S., and POTTINGER, D.: Studies in malaria with special reference to treatment. Part XII. Further researches into the treatment of chronic benign tertian malaria with plasmoquine and quinine, Indian Jr. Med. Research, 1930, xvii, 793-814.

terranean area; and by Most et al.<sup>2</sup> in American troops infected in both the Mediterranean and Pacific theaters. The latter reported relapse rates (clinical or parasitic only) of 89 per cent in 75 cases (all from the Pacific areas) treated with quinine alone; of 84 per cent in 69 cases treated with quinacrine (atabrine) alone; and of 11 per cent of 72 cases treated simultaneously with quinine and pamaquine. (These drugs are not effective if given successively.) The effective doses of pamaquine (.03 to .06 gm. per day), however, caused more or less troublesome toxic reactions in many of the cases, and it would be too dangerous to use except under close medical supervision.

In recent experiments carried out under more rigorous conditions by Berliner et al.<sup>3</sup> the results were less striking but still confirmatory, since five of 18 cases were cured and only two of the others suffered a second relapse.

Pamaquine in full doses will also destroy sporozoites and prevent infection with vivax (and also falciparum) malaria, if it is started the day before experimental infection and continued for a week afterwards. This was shown by James et al.<sup>4</sup> and has been confirmed by Jones et al.,<sup>5</sup> although not all of their cases were protected. The doses required (about .06 gm. per day), however, were far too toxic to warrant its use as a prophylactic agent.

The second important addition to the antimalarial drugs (1930) was atabrine (atebrin, mepaquine), now commonly termed "quinacrine." In brief quinacrine resembles quinine qualitatively in its action and is subject to the same limitations as to its effectiveness. Quantitatively it is more potent as a suppressive and temporarily curative agent, and it is less toxic.<sup>6</sup> No synergistic effect is obtained if quinacrine is combined with quinine. Berliner et al.<sup>3</sup> include in a table four cases of vivax malaria treated with quinacrine and pamaquine concurrently, none of whom relapsed within 10 to 11 months, but they make no comment because the number of observations is so small. It has been generally believed that the administration of quinacrine markedly increases the toxicity of pamaquine, and this is confirmed by Craige et al.<sup>16</sup> (1947) who observed four relapses in five cases so treated. This combination is probably too dangerous to use, even if a synergistic action were demonstrated.

Much of the work done in this country under the guidance of the Board for the Coördination of Malarial Studies was carried out on volunteers who were inmates of the Illinois State Penitentiary at Stateville. These were healthy young adults who were from a nonendemic area and who had not had malaria or an opportunity to develop any immunity from infection.

<sup>2</sup> MOST, H., et al.: Combined quinine-plasmochin treatment of vivax malaria: effect on relapse rate, *Am. Jr. Med. Sci.*, 1946, ccxii, 550-560.

<sup>3</sup> BERLINER, R. W., et al.: Studies on the chemotherapy of the human malaras. VII. The antimalarial activity of pamaquine, *Jr. Clin. Invest.*, 1948, xxvii, supplementary number, May, part 2, 108-113.

<sup>4</sup> JAMES, S. P., NICOL, W. D., and SHUTE, P. G.: On prevention of malaria with plasmoquine, *Lancet*, 1931, ii, 341-342.

<sup>5</sup> JONES, R., JR., et al.: A study of the prophylactic effectiveness of several 8-aminoquinolines in sporozoite-induced vivax malaria (Chesson strain), *Jr. Clin. Invest.*, 1948, xxvii, supplementary number, May, part 2, 6-11.

The experiments were restricted to a few strains of malarial parasites which had been carefully studied, particularly a strain ("Chesson") of vivax malaria from the Pacific area which had an unusual capacity to cause repeated relapses at short intervals. The technic of the experiments was carefully standardized in every detail, so that the results of many series of experiments were truly comparable. Infection was induced in the natural manner by bites of infected mosquitoes. Many new compounds were synthesized, resembling in chemical structure drugs known to be effective. Those which showed most promise on the basis of curative experiments in avian malaria and tests for toxicity in mammals were similarly studied in human infections. A very few of these which promise to be of practical value will be discussed briefly.

Eighteen compounds were tried<sup>7</sup> which resemble pamaquine in being 8-aminoquinolines. Of these, the best was pentaquine. This drug (like pamaquine) destroyed the sporozoites and completely prevented infection in nine of 10 cases.<sup>8</sup> Of six subjects who developed malaria in spite of the prophylactic use of a drug of this series, four were cured by suppressive drugs (like quinine) which ordinarily are not effective in preventing relapse. Evidently these drugs injured the parasites significantly although not killing them. The dose of pentaquine required to protect, 120 to 180 mg. a day, although less toxic than pamaquine, was still too toxic to permit its use as a prophylactic agent.

Pentaquine is about as effective as quinine in terminating an acute attack of malaria. Its effect is greatly enhanced by the simultaneous administration of quinine. Of 26 subjects with vivax infections of moderate severity, treated with 60 mg. of pentaquine base and 2 gm. of quinine daily for 14 days, only one relapsed, and of 17 cases with severe infections, only three relapsed. Cases with massive infections were not protected from relapse.<sup>8</sup> In these doses some toxic symptoms occurred, but they did not necessitate stopping treatment. Close medical supervision, however, is essential. Smaller, less toxic doses may well prove more practicable for use under ordinary conditions, even though the relapse rate may be slightly higher.

A series of 4-aminoquinolines resembling quinacrine in their structure and activity was also synthesized, and 10 of these were tested on human volunteers by Berliner et al.<sup>9</sup> Of these the best was chloroquine, whose activity was about three times that of quinacrine. Most et al.<sup>10</sup> have reported the results of treatment in 365 cases of vivax malaria in military personnel

<sup>6</sup> TAGGERT, J. V., et al.: Studies on the chemotherapy of the human malarias. V. The antimalarial activity of quinacrine, *Ibid.*, 93-97.

<sup>7</sup> ALVING, A. S., et al.: The clinical trial of 18 analogues of pamaquin [sic] (plasmochin) [sic] in vivax malaria (Chesson strain), *Ibid.*, 34-45.

<sup>8</sup> ALVING, A. S., et al.: Pentaquine (SN-13,276), a therapeutic agent effective in reducing the relapse rate in vivax malaria, *Ibid.*, 25-33.

<sup>9</sup> BERLINER, R. W., et al.: Studies on the chemotherapy of the human malarias. VI. The physiological disposition, antimalarial activity, and toxicity of several derivatives of 4-aminoquinoline, *Ibid.*, 98-107.

<sup>10</sup> MOST, H., et al.: Chloroquine for treatment of acute attacks of vivax malaria. *Jr. Am. Med. Assoc.*, 1946, cxxxix, 963-967.



returned to the United States. As these drugs are stored in the tissues, to get an effective concentration in the blood promptly it is necessary to give a large "priming" dose the first day. The regime recommended consists of two doses (or three<sup>11</sup>) of 0.3 gm. the first day, followed by one dose (0.3 gm.) on each of the succeeding three days. Satisfactory results were also reported following 1.2 gm. in divided doses over a period of 24 hours. These doses are practically nontoxic. All but 2 per cent were afebrile after 24 hours, and films were negative after 48 to 72 hours. Falciparum malaria was cured, but in vivax malaria relapses occurred in about 70 per cent of cases from the Pacific area and in about 35 per cent from the Mediterranean. There is as yet no evidence of a synergistic action when chloroquine is administered with pamaquine. Craige et al.<sup>16</sup> reported four relapses in five cases of vivax infection so treated. Further study of this point is desirable. Chloroquine is effective as a suppressive agent in dose of 0.3 gm. once a week, but it does not prevent infection.

Paludrine, a synthetic biguanidine derivative, is a highly promising drug which was produced and studied by a group of British investigators.<sup>12</sup> It is highly effective in terminating an acute attack of either vivax or falciparum malaria. It will cure falciparum malaria, but cases of vivax infection are prone to relapse, and in this respect it is no better than quinacrine or chloroquine. No synergistic effect was obtained in small series of cases when paludrine was combined with quinine<sup>13</sup> or with pentaquine.<sup>8</sup> It is effective in very small doses. A total dose of 50 to 150 mg. usually sufficed to terminate an acute attack, and 12.5 mg. were effective in some cases. On the other hand, 1.5 gm. per day was administered to some subjects without notable toxic effects. Paludrine appears to be virtually nontoxic in full therapeutic doses.

Its greatest value may prove to be its effectiveness as a prophylactic and suppressive agent.<sup>14</sup> It is a true prophylactic for falciparum malaria, 0.1 gm. per day entirely preventing infection in individuals heavily exposed under natural conditions. Volunteers were similarly protected by a single dose of 1 gm. given three hours before experimental inoculation with mosquitoes. It was equally effective as a suppressive agent in vivax infections, apparently by inhibiting the development of the parasites in the tissue phase without eliminating them. As long as the drug was administered (to individuals who had been exposed to infection while under prophylactic treatment) no symptoms were manifested and no parasites could be demonstrated in the blood, even by transfusion experiments, but clinical malaria developed after the drug was stopped.

<sup>11</sup> LOEB, R. F., et al.: Activity of a new antimalarial agent, chloroquine (SN 7618) (Approved statement), *Jr. Am. Med. Assoc.*, 1946, cxxx, 1069-1070.

<sup>12</sup> MAEGRAITH, B. G., et al.: Paludrine in the treatment of malaria, *Brit. Med. Jr.*, 1946, i, 903-905.

<sup>13</sup> JONES, R., JR., et al.: The therapeutic effectiveness of large doses of paludrine in acute attacks of sporozoite-induced vivax malaria (Chesson strain), *Jr. Clin. Invest.*, 1948, xxvii, supplementary number, May, part 2, 51-55.

<sup>14</sup> FAIRLEY, N. H., et al.: Researches on paludrine (N. 4888) in Australia, *Med. Jr. Australia*, 1946, i, 234-236.

These observations have been confirmed in the main by the American group, including Earle et al.<sup>15</sup> They conclude: "The high order of anti-malarial activity shown by paludrine against more than a single phase of the malaras, i.e., primary tissue phase of falciparum and erythrocytic phases of vivax and falciparum, places the drug in a unique position among the synthetic antimalarials developed in recent years.

"Paludrine is the most active suppressive agent in vivax malaria yet described, exceeding quinacrine or chloroquine to a considerable extent in this respect.

"It is less active as a suppressive in falciparum malaria, routine suppression at low dosage being due presumably to its high order of prophylactic action in this infection."

One may conclude that chloroquine is clearly superior to quinine and quinacrine in the treatment of an acute attack of malaria, both in effectiveness and in lesser toxicity. Chloroquine seems to be a little more effective than paludrine, in that it terminates the attack somewhat more quickly. Both will cure falciparum malaria, but neither prevents relapses in vivax infections. Because of its almost complete lack of toxicity, paludrine may prove to be the most useful of these drugs under ordinary conditions. Paludrine appears to be distinctly superior to all the other drugs as a prophylactic and suppressive agent. To cure permanently cases of relapsing vivax malaria, the most effective measure at present is the simultaneous administration of quinine and pentaquine. Because of their toxicity, however, this must be done under close supervision, preferably in a hospital, and it is not advised as a routine procedure. A truly ideal antimalarial drug has not yet been found.

P. W. C.

<sup>15</sup> EARLE, D. P., JR., et al.: Studies on the chemotherapy of the human malaras. X. The suppressive antimalarial effect of paludrine, Jr. Clin. Invest., 1948, xxvii, supplementary number, May, part 2, 130-133.

<sup>16</sup> CRAIGE, B., JR., et al.: Clinical standardization of pamaquin [sic] (plasmochin) [sic] in mosquito-induced vivax malaria, Chesson strain, Am. Jr. Trop. Med., 1947, xxvii, 309-315.

## REVIEWS

*Brief Psychotherapy: A Handbook for Physicians on the Clinical Aspects of Neuroses.* By BERTRAND S. FROHMAN, M.D., with the collaboration of EVELYN P. FROHMAN; foreword by WALTER C. ALVAREZ, M.D. 265 pages; 14 × 20.5 cm. Lea and Febiger, Philadelphia. 1948. Price, \$4.00.

This book has been written ostensibly for the benefit of the non-psychiatric physician, to help him treat his neurotic patients. More than two-thirds of the volume presents a simplified description and discussion of the common neuroses, their etiology and their mechanisms. This part is too simplified and contains so many inaccurate statements which do not fit accepted psychiatric theory that the reviewer feels the book would mislead rather than aid the practicing physician. The remainder describes methods of brief treatment which would take years of training and specialized experience for a therapist to use successfully. For these reasons this book is not "A Handbook for Physicians" as the sub-title indicates.

H. W. N.

*Medical Writing: The Technic and the Art.* 2nd Ed. By MORRIS FISHBEIN, M.D., with the assistance of JEWEL F. WHELAN, Assistant to the Editor. x plus 292 pages; 23.5 × 15.5 cm. 1948. The Blakiston Company, Philadelphia. Price, \$4.00.

Physicians and scientific writers who have had constant use for the first edition of this book, published ten years ago, will welcome the enlarged and revised second edition. Developed as a result of experience with the many manuscripts and periodicals published by the American Medical Association, the material includes help in the construction, preparation and revision of the manuscript, spelling, style and proof-reading. The chapter on "Indexing" is new, and that on "Illustrations" has been extensively revised.

Not only will the physician who prepares articles for publication want this book for reference, but he will find it interesting reading as well.

M. L. W.

*The Contemporary American Family.* By ERNEST R. GROVES and GLADYS HOAGLAND GROVES. 838 pages; 15 × 22.5 cm. J. B. Lippincott Co., Philadelphia. 1947. Price, \$4.50.

The late Dr. Groves and Mrs. Groves designed this comprehensive study, "The Contemporary American Family," to be useful to the reader in his personal career. The book is pedagogic, yet palatable. In surveying their subject through the eyes of history, psychology, sociology, law, biology, mental hygiene, home economics, and education, the authors sacrificed clarifying detail for breadth of scope. It would be useful as a college textbook and for beginning students who wish to study the American Family.

H. W. N.

*The Development of Inhalation Anesthesia (with Special Reference to the Years 1846-1900).* By BARBARA M. DUNCUM, Nuffield Department of Anesthetics, University of Oxford. 640 pages; 14.5 × 23 cm. Oxford University Press, New York. 1947. Price, \$12.00.

This book, after a brief introduction which outlines and correlates the body of the text, presents a detailed account of the history of inhalation anesthesia from the

middle of the 16th century to the beginning of the modern era in the first decade of the 20th century.

The author, after touching upon the early experiments of Harvey and von Helmont on the physiology of respiration, discusses briefly the discoveries of oxygen, carbon dioxide, nitrous oxide, etc., and then enlarges upon the important work of W. T. G. Morton, James Simpson, Horace Wells and Crawford Long. Following this, and in great detail, the problems and controversial issues regarding the use of ether on the one hand and chloroform on the other are discussed, along with the efforts of all men interested in anesthesia to develop other and more perfect agents and technics.

Especially interesting are the excellent illustrations and descriptions of apparatus, and the original correspondence and reports of such men as John Snow, James Simpson and Joseph Clover, pioneers in anesthetic specialization.

This book, because of its great detail, rather than in spite of it, makes absorbing reading.

A. T. N.

### BOOKS RECEIVED

Books received during August are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Advances in Pediatrics.* Volume III. Editorial Board: S. Z. LEVINE, Cornell University Medical College; ALLAN M. BUTLER, Harvard Medical School; L. EMMETT HOLT, JR., New York University, College of Medicine; and A. ASHLEY WEECH, University of Cincinnati, College of Medicine. 363 pages; 24 × 16 cm. 1948. Interscience Publishers, Inc., New York. Price, \$7.50.

*Bacterial and Virus Diseases: Antisera, Toxoids, Vaccines and Tuberculins in Prophylaxis and Treatment.* By H. J. PARISH, M.D., F.R.C.P.E., D.P.H., Clinical Research Director, Wellcome Foundation, Ltd., etc. 168 pages; 19 × 12.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$2.75.

*Breast Feeding: A Guide to the Natural Feeding of Infants.* By F. CHARLOTTE NAISH, B.A., M.B., B.Ch. (Cantab.) 151 pages; 19 × 13 cm. 1948. Oxford University Press, New York. Price, \$3.50.

*Essentials of Pathology.* 3d Ed. By LAWRENCE W. SMITH, M.D., F.C.A.P., Formerly Professor of Pathology, Temple University School of Medicine, etc., and EDWIN S. GAULT, M.D., F.C.A.P., Associate Professor of Pathology and Bacteriology, Temple University School of Medicine. With a Foreword by the late JAMES EWING, M.D., Memorial Hospital, New York City. 764 pages; 27.5 × 21 cm. 1948. The Blakiston Company, Philadelphia. Price, \$12.00.

*An Index of Treatment by Various Writers.* 13th Ed., Revised. Edited by SIR ROBERT HUTCHISON, Bt., M.D., LL.D., F.R.C.P., Consulting Physician, London Hospital, etc.; Assisted by REGINALD HILTON, M.A., M.D., F.R.C.P., Physician to St. Thomas's Hospital, etc. 972 pages; 26 × 17 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$17.00.

*Major Endocrine Disorders.* 2nd Ed. By S. LEONARD SIMPSON, M.A., M.D. (Cantab.); F.R.C.P. (London), Physician, Wilkesden General Hospital, with Charge of Diabetic and Endocrine Clinics, etc. Foreword to the First Edition by the late SIR WALTER LANGDON-BROWN, M.A., M.D. (Cantab.); F.R.C.P. (London), Emeritus Professor of Physics in the University of Cambridge. 552 pages; 22.5 × 14 cm. 1948. Oxford University Press, New York. Price, \$14.00.

- Manual of Leprosy.* By ERNEST MUIR, C.M.G., C.I.E., M.D., F.R.C.S., Edin., Medical Adviser, British Empire Leprosy Relief Association, etc. 208 pages; 22 × 14 cm. 1948. The Williams and Wilkins Company, Baltimore. Price, \$5.00.
- Medical Writing: The Technic and the Art.* 2nd Ed. By MORRIS FISHBEIN, M.D., with the assistance of JEWEL F. WHELAN, Assistant to the Editor. x plus 292 pages; 23.5 × 15.5 cm. 1948. The Blakiston Company, Philadelphia. Price, \$4.00.
- More Than Armies: The Story of Edward H. Cary, M.D.* By BOOTH MOONEY. With an Introduction by DR. MORRIS FISHBEIN. vii plus 275 pages; 22.5 × 15 cm. 1948. Mathis, Van Nort & Company, Dallas. Price, \$5.00.
- Recent Advances in Anaesthesia and Analgesia (Including Oxygen Therapy).* 6th Ed. By C. LANGTON HEWER, M.B., B.S. (Lond.), M.R.C.P. (Lond.), D.A. (Eng.), Senior Anaesthetist, St. Bartholomew's Hospital, etc. 380 pages; 21 × 14 cm. 1948. The Blakiston Company, Philadelphia. Price, \$6.00.
- The Social Medicine of Old Age: Report of an Inquiry in Wolverhampton.* By J. H. SHELDON, M.D. (London), F.R.C.P. (London), Director of Medicine, The Royal Hospital, Wolverhampton. 239 pages; 21.5 × 14 cm. (paper-bound). 1948. Oxford University Press, New York. Price, \$2.00.
- Standards for the Diagnosis and Treatment of Cancer.* By THE CANCER COMMITTEE OF THE IOWA STATE MEDICAL SOCIETY. 160 pages; 23.5 × 15.5 cm. (stiff-paper back). 1948. Iowa State Medical Society, Cedar Rapids. Price, \$1.00.
- The Treatment of Malignant Disease by Radium and X-Rays, Being a Practice of Radiotherapy.* By RALSTON PATERSON, M.C., M.D., F.R.C.S.E., D.M.R.E., F.F.R., Christie Hospital and Holt Radium Institute, Manchester. 622 pages (and charts); 25 × 17 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$11.00.
- Tuberculosis in the British Zone of Germany, with a Section on Berlin. Report of an Inquiry Made in September-October, 1947.* By M. DANIELS, M.D., D.P.H., and P. D'ARCY HART, M.D., F.R.C.P., Members of the Scientific Staff Medical Research Council. 32 pages (and 37 pages in Berlin section); 24.5 × 15.5 cm. (paper-bound). 1948. His Majesty's Stationery Office, London. Price, Sixpence net.
- Zinsser's Textbook of Bacteriology: The Application of Bacteriology and Immunology to the Diagnosis, Specific Therapy and Prevention of Infectious Diseases for Students and Practitioners of Medicine and Public Health.* 9th Ed. Revised by DAVID T. SMITH, M.D., Professor of Bacteriology and Associate Professor of Medicine, Duke University School of Medicine; DONALD S. MARTIN, M.D., M.P.H., Professor of Preventive Medicine and Public Health and Associate Professor of Bacteriology, Duke University School of Medicine; NORMAN F. CONANT, Ph.D., Professor of Mycology and Associate Professor of Bacteriology, Duke University School of Medicine; JOSEPH W. BEARD, M.D., Professor of Surgery in Charge of Experimental Surgery, Duke University School of Medicine; GRANT TAYLOR, M.D., Associate Professor of Bacteriology and Associate Professor of Pediatrics, Duke University School of Medicine; HENRY I. KOHN, Ph.D., M.D., Surgeon U. S. P. H. S., Assistant Professor of Physiology and Pharmacology (on leave), Duke University School of Medicine; and MARY A. POSTON, M.A., Instructor in Bacteriology, Duke University School of Medicine. 992 pages; 25.5 × 17 cm. 1948. Appleton-Century-Crofts, Inc., New York. Price, \$10.00.

# COLLEGE NEWS NOTES

## A.C.P. POSTGRADUATE COURSES, AUTUMN 1948

At this date (September 13, 1948) the Autumn schedule of courses is well launched.

Course No. 1, **CARDIOLOGY**, at the National Institute of Cardiology of Mexico, under Dr. Ignacio Chavez, F.A.C.P., Director, has been concluded. Twenty-three American physicians were registered, many were accompanied by members of their families, and arrangements were made for a combined postgraduate course and vacation. Dr. E. L. Bortz, F.A.C.P., Philadelphia, Chairman of the Advisory Committee on Postgraduate Courses, was in attendance throughout the period. The physical accommodations were superior to those of any institution where similar courses have been given previously. The course was so arranged that approximately one-half of the morning was devoted to didactic teaching and one-half to clinical teaching in groups of three or four physicians. Dr. George R. Herrmann, F.A.C.P., Professor of Medicine at the University of Texas School of Medicine, was a guest teacher from the States. All the Mexican teachers spoke English so there were no language difficulties. Reports from the registrants in the course indicate superb arrangements and most excellent teaching, with great credit going to the Director, Dr. Chavez. It is hoped that with this excellent beginning, the College will arrange not only to repeat this course but to schedule other courses occasionally in Mexico City.

Course No. 2, **INTERNAL MEDICINE WITH EMPHASIS ON PATHOLOGICAL PHYSIOLOGY**, September 13-18, at the University of Cincinnati College of Medicine under Dr. M. A. Blankenhorn, F.A.C.P., Director, was over-subscribed and a number of members, and many non-members, who wished to take the course could not be accommodated this year. That course is at this time still in progress.

Course No. 3, **INTERNAL MEDICINE**, September 20-October 2, at the University of Pittsburgh Medical Center under Dr. R. R. Snowden, F.A.C.P., Director, was first scheduled for a maximum of 25, but demand was so great among members of the College for this course, which has already developed an outstanding reputation from previous years, that arrangements were made whereby the number could be increased to 47.

Course No. 4, **INTERNAL MEDICINE**, October 18-29, at the University of Michigan Medical School under Dr. Cyrus C. Sturgis, F.A.C.P., Director, is at this time still in process of registration. It is anticipated that a very satisfactory registration will develop for this course.

Course No. 5, **ENDOCRINOLOGY**, November 1-6, under the auspices of the University of Illinois College of Medicine, but with headquarters at the LaSalle Hotel, Chicago, is still in the process of registration and there are facilities available for a number more registrants. A group of as many as 100 can be accommodated. This course has been given by the College on several previous occasions and has always been an outstanding success. It includes an intensive review of new developments in the field of endocrinology, special attention to be paid to clinical disorders. Physiological and biochemical developments will be presented in relation to their bearing on the interpretation of clinical phenomena. A great host of institutions and societies are represented on the faculty; in fact, there probably has never before been a course offered by the College with such an array of teachers from all over the U. S. and Canada. Detailed outlines of all features of the course are available and those interested should register immediately. Hotel and other accommodations are adequately available.

Course No. 6, **RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE**, November 15-24, at the Massachusetts General Hospital under

Drs. Paul D. White, F.A.C.P., Howard B. Sprague, F.A.C.P., and Edward F. Bland, Directors, as usual, has been filled to capacity for some weeks. In fact, the maximum accommodations were increased from 90 to 100 and even then a very large number of late applicants could not be accommodated. The reputation of this course is expanding far beyond the U. S. and Canada as evidenced by applications from European countries, India, Puerto Rico and elsewhere. Those who could not be accommodated this year will be placed on a waiting list to receive preference for registration the next time this course is given, presumably in the Autumn of 1949.

Course No. 7, **CARDIOVASCULAR DISEASE**, December 6-11, at Emory University School of Medicine, Atlanta, Ga., under Dr. R. Bruce Logue, F.A.C.P., Director, is still in the course of registration. The maximum number that can be accommodated has been raised from 50 to 75. The local faculty will be ably assisted by Dr. Eugene A. Stead, Jr., F.A.C.P., Professor of Medicine at Duke University School of Medicine, and by Dr. Richard L. Riley, Research Associate, Columbia University College of Physicians and Surgeons, New York. During recent years, a considerable knowledge of the cardiovascular system has accumulated through the use of newer technics, such as catheterization and contrast visualization, as well as studies with the use of radioactive isotopes. The practical application of the studies will be given and a brief survey of electrocardiography with emphasis on recent developments will be included. Detailed outlines of this course are available on request. The course is a very excellent one in its field and a tribute to the fine work being done at this southern institution.

Course No. 8, **GASTRO-ENTEROLOGY**, December 6-11, at the Graduate Hospital of the University of Pennsylvania, Philadelphia, under Dr. Henry L. Bockus, F.A.C.P., Director, was originally scheduled for a maximum number of 55 physicians. The demand has been so great that a careful survey revealed that a larger number could be accommodated and the Director is prepared now to accommodate 100 registrants. The course includes a survey of recent and significant developments in gastro-enterology. Emphasis throughout the course will be placed on gastrointestinal physiology, biochemistry and pathology. There will be didactic presentations, conferences, case reports, and panel discussions. Features have been carefully selected and the instructors will be members of the faculties of many nearby medical schools in addition to those on the faculty of the University of Pennsylvania. The Director is a most capable and inspiring teacher.

Address all inquiries and applications for registration to Mr. E. R. Loveland, Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

#### A.C.P. REGIONAL MEETINGS

1948-49

<i>Date</i>	<i>Territory</i>	<i>Place</i>	<i>Chairman</i>
July 25	Mississippi	Jackson, Miss.	John G. Archer, M.D., <i>Governor</i>
September 11	North Dakota	Fargo, N. D.	R. B. Radl, M.D., <i>Governor</i>
September 25	Oklahoma	Tulsa, Okla.	Wann Langston, M.D., <i>Governor</i>
September 29	Western Pennsylvania	Pittsburgh, Pa.	R. R. Snowden, M.D., <i>Governor</i>
October 20	Western New York	Syracuse, N. Y.	E. C. Reifenstein, M.D., <i>Governor</i>

October 30	Arkansas	Hot Springs, Ark.	Arless A. Blair, M.D., <i>Governor</i>
November 5	New Jersey	Newark, N. J.	George H. Lathrope, M.D., <i>Governor</i>
November 12-13	NORTHWEST: Washing- ton, Oregon, Wyom- ing, Alberta, British Columbia, Manitoba, Saskatchewan, Idaho, Montana	Vancouver, B. C.	G. F. Strong, M.D., <i>Regent</i>
November 20	MIDWEST: Michigan, Il- linois, Indiana, Wis- consin	Detroit, Mich.	Douglas Donald, M.D., <i>Governor</i>

In addition, Regional Meetings are being planned for Iowa in October, the exact date and place yet to be determined by B. F. Wolverton, M.D., Governor; for Kentucky, under the Governorship of J. Murray Kinsman, M.D., in November or December; and for Maryland and the District of Columbia. Drs. Wetherbee Fort and Wallace M. Yater, Governors for these two territories, respectively, are discussing the possibility of holding the meeting this year in Washington, D. C. Place and date will be announced later.

The program of the Western Pennsylvania Regional Meeting included scientific sessions in the morning and afternoon at the Western State Psychiatric Institute and Clinic, and an evening session at the Pittsburgh Athletic Association Annex. The morning symposium concerned Rheumatic Fever, and the participants were Frank J. Gregg, M.D., F.A.C.P., Grace S. Gregg, M.D., and J. J. McAleese, M.D., all of Pittsburgh. The afternoon session offered a symposium on Viruses and Virus Diseases, with discussions by Byron L. Bennett, (MC), USA, Ret'd, Max A. Lauffer, Ph.D., W. Conway Price, Ph.D., and Jonas E. Salk, M.D., all of Pittsburgh. Cocktails and a banquet followed, with musical offerings and remarks by the local Governor, R. R. Snowden, M.D., F.A.C.P., by Edward L. Bortz, M.D., F.A.C.P., Governor for Eastern Pennsylvania, by William S. McEllroy, M.D., F.A.C.P., Dean of the University of Pittsburgh School of Medicine, and by E. R. Loveland, A.C.P. Executive Secretary.

Members of the College from Western New York met on October 20 at the Syracuse University College of Medicine and the Onondaga Golf and Country Club. The following papers were presented in the scientific sessions: Basic Studies with Vitamin E, by John R. Williams, Sr., M.D., F.A.C.P., Rochester; Pitfalls in the Diagnosis of Diabetes, Bernard A. Watson, M.D., F.A.C.P., Clifton Springs; Vaso-depressor Properties of Morphine when Administered Following Hypotension, Richard Lee, M.D., Syracuse; Bacterial Endocarditis with Emphasis on Escherichiae-Aerobacter Group as the Infective Organism, C. Stewart Wallace, M.D., Associate, Ithaca; Detection of Blocking Antibody by the Direct Method in Patients with Ragweed Hay Fever, William G. Woodin, M.D., Syracuse; Significance of Axis Deviation, George H. Reifstein, M.D., Associate, Syracuse; Results of Cardiorespiratory Functional Studies in Cases of Beryllium Granulomatosis of the Lung, Robert Bruce, M.D., Rochester; Significance of Human Adrenal Cholesterol in Relation to Adrenal Function and Morphology, Walter F. Rogers, M.D., Syracuse; Utilization of Human Albumin, Christine Waterhouse, M.D., Rochester; Changes in Peripheral Blood Flow after Sympathetic Blockade and Sympathectomy, Richard H. Lyons, M.D., F.A.C.P., Syracuse; Renal Factors in the Formation of Edema, Robert F. Pitts, M.D., F.A.C.P., Syracuse; Multiple Angiomata of the Lungs Simulating Congenital Heart Disease, William S. McCann, M.D., F.A.C.P., Rochester; Diagnosis and Treatment of Gouty Arthritis, John H. Talbott, M.D., F.A.C.P., Buffalo. The papers presented were



discussed by A.C.P. President Walter W. Palmer, of New York City, following which J. Howard Ferguson, M.D., of Syracuse, led a clinical pathological conference, with discussion by Edward N. Packard, M.D., F.A.C.P., Trudeau, and Frederick T. Schnatz, M.D., F.A.C.P., Syracuse. Dr. Palmer was the chief speaker in the evening, but brief remarks were made also by Dr. McCann, Dr. Asa L. Lincoln, Governor for Eastern New York, Dr. H. G. Weiskotten, Dean of Syracuse University College of Medicine, and Mr. E. R. Loveland, Executive Secretary.

At the time of this writing, only the tentative program of the Northwest Regional Meeting, Vancouver, B.C., November 12-13, can be given. Papers were presented by the following physicians, in the Vancouver General Hospital: Cardiac Complications of Infectious Mononucleosis, Hance F. Haney, M.D., Associate; Hiatus Hernia, John H. Fitzgibbon, M.D., F.A.C.P.; Sarcoidosis, John J. Krygier, M.D., Associate; Inhibitory Hormone of the Testicle, Ben Vidgoff, M.D., Associate; Congestive Heart Failure, Particularly Splenomegaly in That Condition, Isidor C. Brill, M.D., F.A.C.P.; Discussion of the Lymphomatous Diseases, Russel L. Baker, M.D., F.A.C.P.; Use of Vitamin E in Arteriosclerotic Heart Disease, Homer P. Rush, M.D., F.A.C.P.; all of Portland, Ore.; Ankylosing Spondylitis, Kenneth A. Hamilton, M.D., F.A.C.P., Edmonton, Alta.; Medical Aspects of Atomic Energy, Stafford L. Wafren, M.D., Los Angeles, Calif.; Primary Tuberculous Skin Infection from a Swimming Pool, Donald E. H. Cleveland, M.D., F.A.C.P.; Somatic or Psychic?, George A. Davidson, M.D., F.A.C.P.; Role of the Failing Heart in Cerebral Thrombosis, George F. Strong, M.D., F.A.C.P., and Samuel E. C. Turvey, M.D., F.A.C.P.; all of Vancouver, B. C.; Consideration of the Pathology of Pyelonephritis in Application of Therapy, Robert H. Williams, M.D., F.A.C.P.; and Metabolic Aspects of Hypertensive Disease, Daniel M. Green, M.D., F.A.C.P.; both of Seattle, Wash. The sessions were presided over by Dr. Charles E. Watts, F.A.C.P., Seattle, Third Vice President, Dr. John W. Scott, M.D., F.A.C.P., Edmonton, Governor for Alberta and British Columbia, and by the Governor for Washington, Dr. George H. Anderson, M.D., F.A.C.P., of Spokane. Guest speakers listed for the evening session at the Hotel Vancouver included A.C.P. President Walter W. Palmer, of New York, Mr. E. R. Loveland, Executive Secretary, Philadelphia, and Dr. L. R. Donaldson, Associate Professor of Fisheries, University of Washington.

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#### UNIVERSITY OF MICHIGAN ANNOUNCES 1949 POSTGRADUATE COURSE SCHEDULE

Dr. Howard H. Cummings, Chairman and Professor in the Department of Postgraduate Medicine, University of Michigan, announces the following schedule of courses during 1949. Further information can be obtained by addressing Dr. Cummings.

1. Application of the Basic Sciences to Clinical Medicine; January 3-29.
2. Diseases of the Gastro-Intestinal Tract; March 14-18.
3. Metabolism and Endocrinology; March 21-25.
4. Rheumatology and Recent Advances in Therapeutics; March 28-April 1.
5. Diseases of the Heart; April 4-8.
6. Diseases of the Blood and Blood-Forming Organs; April 11-15.
7. Allergy; April 18-22.

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#### UNIVERSITY OF CALIFORNIA AT LOS ANGELES ANNOUNCES POSTGRADUATE COURSE PROGRAM

Dr. S. J. Weinberg (Associate, ACP), Head of Postgraduate Instruction, Medical Extension, University of California, Los Angeles, has announced the program of postgraduate courses for 1948-49, as follows:

INFECTIOUS DISEASES; October 21, 1948–March 31, 1949; Thursdays, 8:00 to 10:00 p.m.  
 DERMATOLOGY IN INTERNAL MEDICINE; January 3–February 21, 1949; Mondays, 8:00 to 10:00 p.m.  
 MEDICINE; September 21–December 7, 1948; Tuesdays, 8:00 to 10:00 p.m.  
 CARDIOLOGY; September 22–December 8, 1948; Wednesdays, 8:00 to 10:00 p.m.  
 PEDIATRICS; September 23–December 2, 1948; Thursdays, 8:00 to 10:00 p.m.  
 ELECTROCARDIOGRAPHY; January 4–20, 1949; Tuesdays and Thursdays, 8:00 to 10:00 p.m.  
 MEDICAL PHOTOGRAPHY; September 20, 1948, four different meeting hours, 8:00 to 10:00 p.m.  
 NEUROPSYCHIATRY FOR THE GENERAL PRACTITIONER; October 1–December 10, 1948; Fridays, 8:00 to 10:00 p.m.  
 SURGICAL PATHOLOGY; to be given during spring of 1949.  
 All courses on the above schedule will be held at Los Angeles.

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#### AMERICAN GOITER ASSOCIATION

The next annual meeting of the American Goiter Association will be held May 26–28, 1949, at the Hotel Loraine, Madison, Wis. The program will include papers on goiter and other diseases of the thyroid gland, dry clinics and demonstrations.

The Van Meter Prize Award of \$300.00 and awards of two honorable mentions will be made for the best essays concerning original work on problems related to the thyroid gland. Competing essays may cover either clinical or laboratory investigations and should be submitted not later than March 15, 1949, as typewritten double space copy, in English, to the Corresponding Secretary, Dr. T. C. Davison, 207 Doctors Building, Atlanta 3, Ga. The papers should not exceed 3,000 words in length.

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#### NATIONAL DIABETES WEEK

December 6–12, 1948

The Committee on Diabetes Detection of the American Diabetes Association has initiated far reaching plans for a National Diabetes Detection Week, December 6–12, 1948. The discovery and treatment of diabetes mellitus at an early stage demands the attention of all practicing physicians. Failure to discover and treat diabetes early results in preventable disabilities and impairments of health. In the Diabetes Exhibit before the last meeting of the American Medical Association at Chicago, it was shown that the mortality rate for diabetics first seen when a complication had occurred was three times the rate for diabetics first seen earlier and before impairments had developed.

Dr. Charles H. Best, as President of the American Diabetes Association, is urging the coöperation of all medical societies, county, state and national, to support the plans for the National Diabetes Week. The National Committee on Diabetes Detection has prepared material containing information on diabetes for use by the physician in his own town. This material includes programs for medical meetings, radio broadcasts and spot radio announcements for use by city and county medical societies, and suggestions for coöperation with local hospitals toward the control of diabetes.

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The Executive Committee of the Menninger Foundation School of Psychiatry (psychiatric teaching division of the Institute of Psychological Medicine) and the Winter Veterans Administration Hospital of Topeka are accepting applications for admission to the School on January 1, 1949, available only to doctors who have had

some psychiatric residency training in an approved hospital, and who can, therefore, qualify for advanced standing. Dr. Karl Menninger is the Chairman of the Dean's Committee of the School, and Dr. William C. Menninger, F.A.C.P., has much to do with the teaching and the direction of the training program.

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According to the minutes of the meeting of the Joint Committee for the Coördination of Medical Activities held in Chicago, June 5, a new specialty board has been organized to establish standards and meet the needs of physicians engaged in full-time careers in preventive medicine and public health. The board will consist of nine members—three from the American Public Health Association, three from the Section on Preventive and Industrial Medicine for Public Health of the American Medical Association, one from the Southern Medical Association, one from the Canadian Public Health Association, and one from the University Schools of Public Health. The new board will be called the American Board of Preventive Medicine and Public Health Physicians.

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#### THE NEW YORK ACADEMY OF MEDICINE CONDUCTS TWENTY-FIRST GRADUATE FORTNIGHT

The Twenty-First Graduate Fortnight of the New York Academy of Medicine was conducted at the Academy Building from October 4 to 15, 1948, on the general subject of "Advances in Therapy." President of the Academy is Dr. George Baehr, F.A.C.P. Dr. Mahlon Ashford, F.A.C.P., was Chairman of the Committee on Hospital Clinics, and Dr. Louis J. Soffer, F.A.C.P., was Chairman of the Committee on Panel Discussions. A large percentage of the speakers on the program were Fellows of the American College of Physicians.

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#### INTERNATIONAL SOCIETY OF INTERNAL MEDICINE

Professor A. Gigon of Basel, Switzerland, who has been active in the plans for the organization of the International Society of Internal Medicine, has reported (September 1, 1948) that the following countries will be represented at the first meeting at Basel, September 27-29: Austria, Belgium, Czechoslovakia, Denmark, Finland, France, Great Britain, Holland, Hungary, Italy, Norway, Portugal, Spain, Sweden, Switzerland, Turkey, United States of America; and, possibly, some South American countries, Australia, Canada, China and India.

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Dr. Thomas T. Holt, of Wichita, the first Fellow of the American College of Physicians from the State of Kansas (1923), retired from active practice July 14, 1948. Dr. Holt was very active in the affairs of the College as College Governor for Kansas from 1929 to 1941, and as Vice President, 1941-42. He was one of the original proponents of each state having its own regional meeting and was very successful in devoting approximately one-half of his program to the basic sciences. This has become an avowed part of the postgraduate program of the College, as represented by various courses given in recent years on the physiologic approach to medicine. Dr. Holt, himself, took approximately 22 postgraduate courses the first half of his medical life, extending from a minimum of one month to one year and taken in the various medical centers of Europe as well as throughout the states.

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F. William Sunderman, M.D., F.A.C.P., has recently been appointed head of the Department of Clinical Pathology of the Cleveland Clinic Foundation. Formerly a member of the Medical Faculty of the University of Pennsylvania School of Medicine and Assistant Director of the University Hospital's Pepper Laboratory, Dr. Sunderman has more recently served as Professor of Clinical Pathology and Director of the

Laboratory of Clinical Medicine in the Temple University Medical School. Dr. Sunderman is a Diplomate of the American Board of Pathology and the American Board of Internal Medicine. He serves as a member of the American Board of Trustees of the American Board of Pathology, a Governor of the College of American Pathologists, and a member of the editorial board of the American Journal of Clinical Pathologists.

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Colonel A. Parker Hitchens, (MC), U. S. A., Ret'd, F.A.C.P., has recently resigned from his position as Health Commissioner, Wilmington, Del., to become Director of the Bureau of Laboratories of the Pennsylvania State Department of Health. His office is located in the Laboratories of Public Health and Preventive Medicine Bldg. on the campus of the University of Pennsylvania.

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Brigadier General Leon A. Fox, (MC), U. S. A., Retired, F.A.C.P., has been honored by a decoration of Honorary Commander of the Order of the British Empire. The citation mentions the valuable assistance which General Fox gave to the British armies as Field Director of U. S. Typhus Commission.

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John D. Battle, M.D., (Associate), Cleveland, has been appointed a member of the staff of the Cleveland Clinic in the Division of Internal Medicine. Dr. Battle graduated from Washington and Lee University in 1934, and received his M.D. degree from the University of Pennsylvania in 1938. A diplomate of the American Board of Internal Medicine, Dr. Battle was a Fellow at the Cleveland Clinic from 1940 to 1942.

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Dr. Robert B. Radl, F.A.C.P., College Governor for North Dakota, was recently appointed to a 3-year term on the State Board of Medical Examiners of North Dakota.

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Dr. Leon Hughes Hetherington, F.A.C.P., heretofore in the Veterans Administration, has been appointed Director of Tuberculosis Services in the State Department of Health in the State of Maryland, effective October 1, 1948, and will have his headquarters at 2411 North Charles Street, Baltimore, Md.

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Harry Warshawsky, M.D., F.A.C.P., resigned from full-time service in the Veterans Administration in June and has since become established in the private practice of internal medicine in Lima, Ohio.

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Brigadier General Henry C. Dooling, F.A.C.P., has recently retired from the U. S. Army and is now Medical Director of State Sanitorium No. 1, South Mountain, Pa.

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Philip Krainin, M.D., F.A.C.P., New York, has been appointed Assistant Clinical Professor of Medicine in the New York Medical College.

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Carrol C. Turner, M.D., F.A.C.P., Memphis, has gained considerable recognition as an amateur photographer. He received the Silver Cup of the American Physicians' Art Association during the recent American Medical Association meeting in Chicago, an honor which he won also in 1946. His rating among salon exhibitors in the 1948 issue of American Annuals of Photography was 23rd and during the last five years he had 291 prints hung in 160 International Salons, making him a "Three Star Exhibitor."

Louis H. Bauer, M.D., F.A.C.P., Hempstead, N. Y., has been elected Executive Secretary of the World Medical Association, the offices of which have been established at the New York Academy of Medicine.

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Glenn E. Drewyer, M.D., F.A.C.P., formerly on the staff of the Glenwood Hot Springs Clinic, Glenwood Springs, Colo., has recently accepted appointment as Clinical Director of the Veterans Administration Center at Bay Pines, Fla. Dr. Drewyer will reside at 206 15th Ave., N. E., St. Petersburg, Fla.

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Dr. Alfred W. Dubbs, F.A.C.P., has recently been appointed as head of the Department of Medicine, Sacred Heart Hospital, Allentown, filling the vacancy created by the death of Dr. Willard D. Kline, F.A.C.P. Dr. Dubbs has been an Associate in Medicine at the Sacred Heart Hospital since 1935, and Director of the Department of Cardiovascular Disease since 1937.

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A very interesting account of the development and organization of a large industrial medical department is given in the Thirtieth Anniversary Issue of The Medical Bulletin of Standard Oil Company (New Jersey) and Affiliated Companies, Vol. 8, No. 2, June, 1948. This number also pays tribute to Willard J. Denno, M.D., F.A.C.P., New York, N. Y., in the following statement.

"Under the constant vigilance and guidance of Dr. Willard J. Denno, the medical department grew during his twenty-seven years of service into a world-wide organization. He has shown what can be done in the medical phase of human relations when the utmost support of Management is received. His greatest contribution to medicine in industry was his broad vision in foreseeing the requirements of a medical department in order for it to assume its proper role in the affairs of a modern-day business enterprise. It is mainly due to his unusual quality of leadership and ability to organize and coördinate the diversified medical activities of the parent organization that the present status of the medical departments has been attained."

## OBITUARIES

## DR. BERTHOLD STEINBACH POLLAK

Dr. Berthold S. Pollak died June 27, 1948, one day after his seventy-fifth birthday, of cerebral arteriosclerosis. He was born June 26, 1873, in Vienna, the son of Theresa and Joseph Pollak, and came to the United States when 15 years old. For three years he was an apprentice in the Philadelphia wholesale drug firm of Bullock and Crenshaw, after which he attended the Philadelphia College of Pharmacy and the University of Pennsylvania. He graduated in Medicine from Dartmouth College in 1895, served as assistant to his uncle, the late Dr. Louis Steinbach, professor of surgery at the Philadelphia Polyclinic Hospital, and subsequently was chief resident physician at the Pottsville Hospital, Pottsville, Pa. In 1896 Dr. Pollak married Miss Henrietta G. Cohn of Pottsville, Pa., who died in 1912. In 1917 he married Miss Louise Gruber of Baltimore, Md., who died in 1937. He leaves two daughters, Mrs. Philip S. Birnbaum of Jersey City and Mrs. Alfred Kruger, wife of Dr. Kruger, of Norfolk, Va., and three grandchildren.

Arriving in Jersey City in 1898, as a young general practitioner, he soon became the physician to many of the most prominent families. Because of his strong personality and unusual oratorical ability, he was promptly recognized as a leading figure in community welfare work. When, in 1907, plans began to develop for a tuberculosis sanatorium in Hudson County, Dr. Pollak was chosen to head it. He was sent abroad to glean from the famous tuberculosis centers the latest and best in diagnosis and treatment. In due time he succeeded in organizing a sanatorium at Secaucus, followed by a chain of diagnostic chest clinics throughout the County that now serve as diagnostic stations for chest diseases. In this capacity they also provide a consultation service to private physicians and cover most of the follow-up in the findings of mass surveys.

With the newer developments in the treatment of tuberculosis Dr. Pollak soon saw the advantages of having a tuberculosis hospital in or near a large city. He felt that not only was the institution nearer the patient's family, but also located where leading specialists were more available. This long-hoped-for desire of his was realized when the new three million dollar tuberculosis hospital was erected in 1937 as the Hudson County Tuberculosis Hospital. In view of his 40 years of devotion and leadership in the fight against tuberculosis this hospital was renamed in his honor in 1946 as the Berthold S. Pollak Hospital for Chest Diseases. Through his efforts the hospital was then opened also to those needing special treatment for chest diseases other than tuberculosis. Until a qualified clinic staff was acquired, he personally looked after many of the clinics, including night clinics while these were in force. He also served as consulting phthisiologist to nearly all the hospitals in Hudson County, the Beth Israel Hospital in Newark, and served as chairman of the Medical Board of Deborah Jewish Consumptive Sanatorium at Browns Mills, N. J.

In 1919, he helped organize the Hudson County Tuberculosis League and, up to his last illness, served as a leading force in its accomplishments. Largely through his efforts in the League and as chairman of the Legislative Committee of the Medical Society of New Jersey, a law was passed in 1939 making tuberculin test of school children mandatory for the first time in this country. This has since practically eliminated tuberculosis in high schools and colleges in New Jersey and created a wholesome tuberculosis consciousness of the public in general with a better understanding of the entire problem.

One of the earliest members of the American College of Physicians, having been elected a Fellow in 1916, Dr. Pollak was also a Fellow of the American Medical Association, a Diplomate of the American Board of Internal Medicine, a past president

of the Hudson County Medical Society, the New Jersey Tuberculosis League, and the New Jersey Public Health and Sanitary Association, and a delegate of the National Tuberculosis Association at conferences of the International Union against Tuberculosis in London, Paris, Lausanne, Brussels, Oslo, Warsaw, Rome, Lisbon and Washington. He was the author of many articles on various phases of early diagnosis and treatment of tuberculosis. In all these activities he displayed broad constructive ideas backed by a ruggedness of body and spirit that enabled him to carry on until the wear and tear of time and physical infirmities began to take their toll.

His public activities were not limited to medical affairs. He was president of Temple Beth-El for over a generation, a founder and director of the Hudson County Hebrew Home for Orphans and Aged, a past president and treasurer of District Grand Lodge No. 3 B'nai B'rith, a life member of the Jersey City Lodge of Elks, a Mason, a member of the Advisory Board of the Salvation Army, director of the Jewish Community Center of Jersey City, and a member of the Advisory Board of Selective Service in World War II.

Throughout his life he fulfilled the highest ideals of citizenship and of the medical profession. He was a firm believer in the brotherhood of man and the Fatherhood of God without distinction as to race, color or creed.

With the death of Dr. Berthold S. Pollak on June 27, there came to an end an era in medicine and public health, especially in tuberculosis, not only in Hudson County but throughout the State. His passing leaves a keen sense of loss in the hearts of his colleagues, co-workers, patients, and all who knew him.

ABRAHAM E. JAFFIN, M.D., F.A.C.P.

### DR. E. ROLAND SNADER, JR.

Dr. Snader was a distinguished physician who has left a lasting mark among his confreres.

Dr. Snader was born in Philadelphia, November 1, 1895. He obtained his B.S. degree at Haverford College and M.D. degree at Hahnemann Medical College of Philadelphia in 1921.

He served in various capacities at Hahnemann and was thought of as a brilliant teacher and a friend of the students. He was Chief Medical Resident, Clinical Assistant, Electrocardiographer, Assistant Physician and Physician at Hahnemann Hospital; Professor of Clinical Medicine in Hahnemann Medical College and Hospital of Philadelphia.

Dr. Snader also was consulting Physician in Internal Medicine at the Allentown State Hospital, the William McKinley Memorial Hospital, Trenton, N. J., the Homeopathic Hospital of Chester County, West Chester, and the J. Lewis Crozer Home for Incurables and Homeopathic Hospital in Chester.

Dr. Snader was Past President of the Homeopathic Medical Society of the County of Philadelphia, and a Past Trustee of the Homeopathic Medical Society of the State of Pennsylvania. He was an interested and diligent worker on the Council of the American Diabetes Association. He was a member of the Philadelphia Medical Club and became a Fellow of the American College of Physicians in 1928. He was a Diplomate of the American Board of Internal Medicine. Dr. Snader is the author of numerous medical papers.

Dr. E. Roland Snader was a forthright, vigorous, jolly, vital gentleman. He was intolerant of all insincerity. He was implicitly trusted by his colleagues and patients, and warmly loved by his many friends.

EDWARD L. BORTZ, M.D., F.A.C.P.,  
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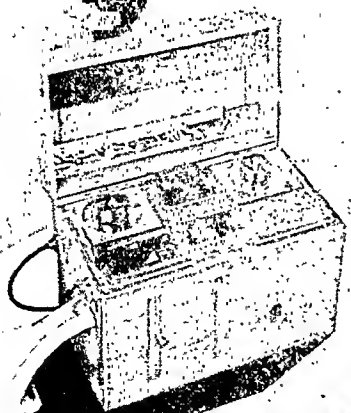
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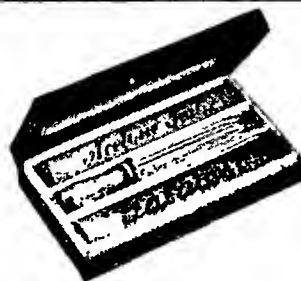
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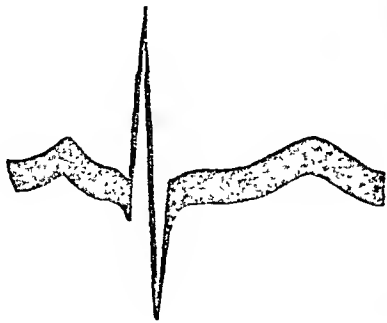
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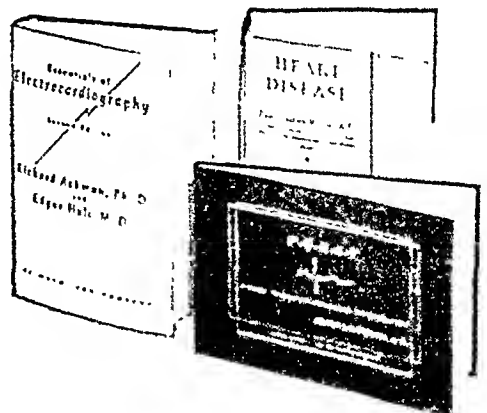
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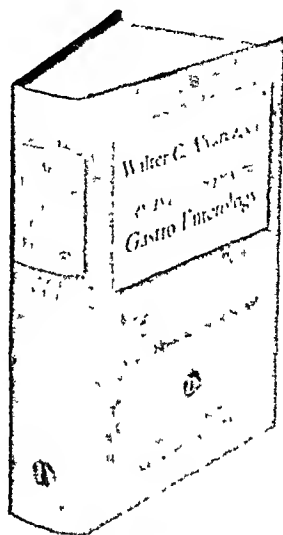


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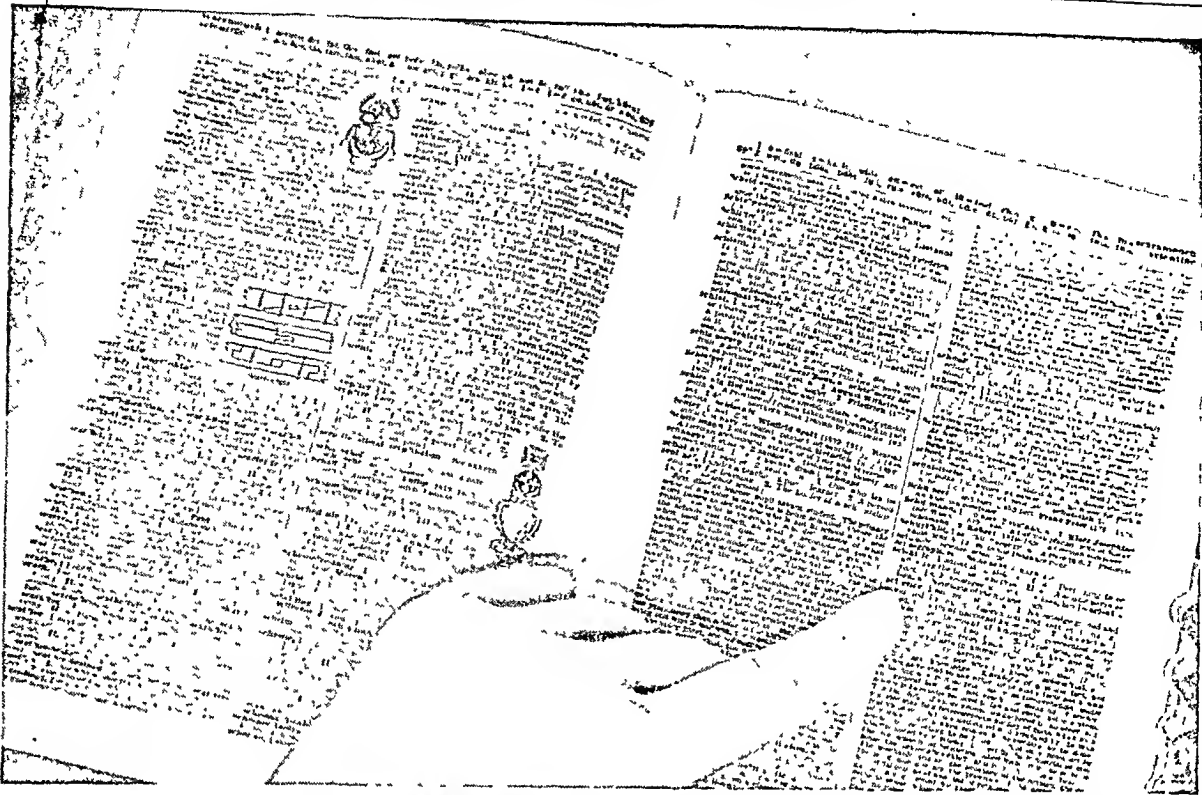
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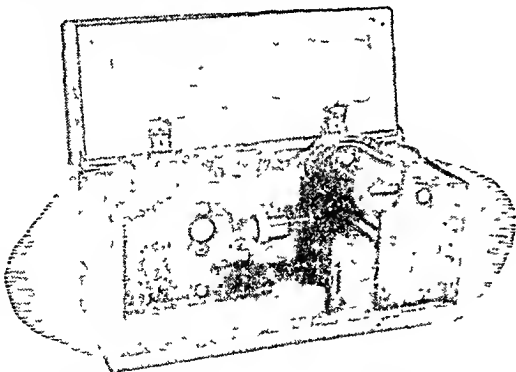
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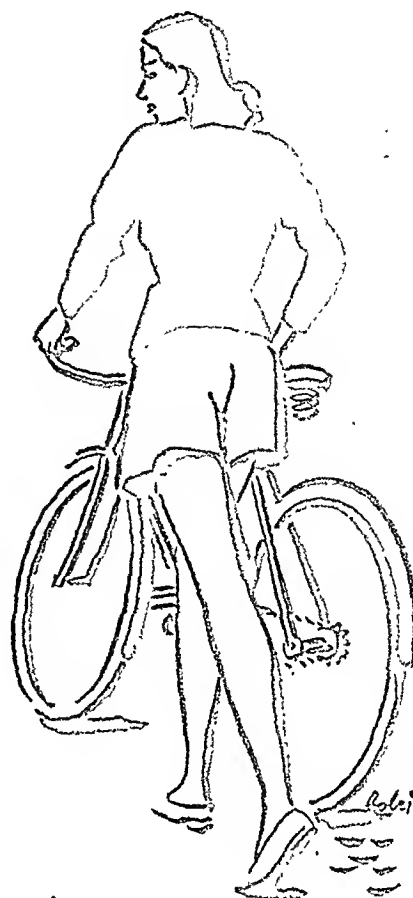
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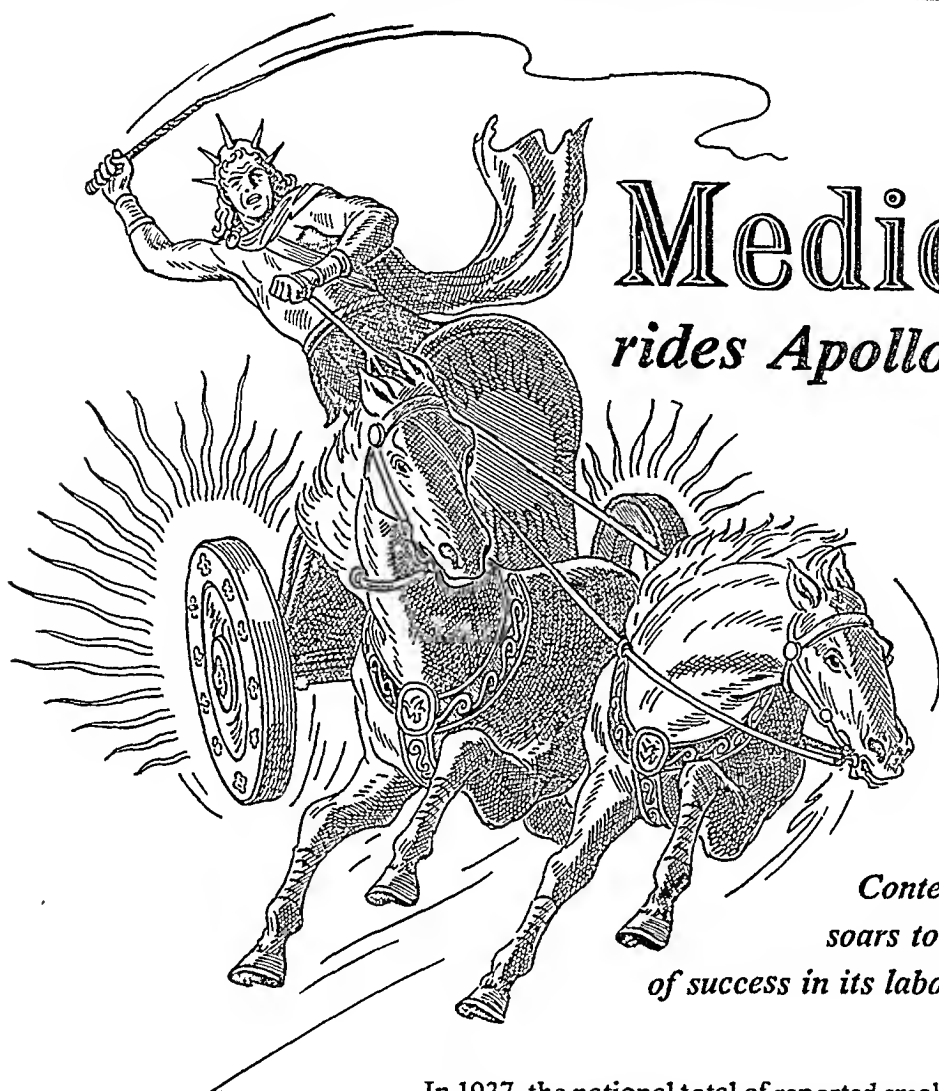
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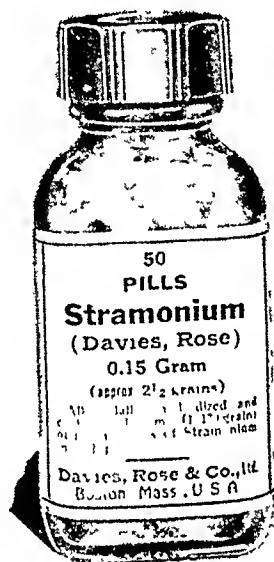
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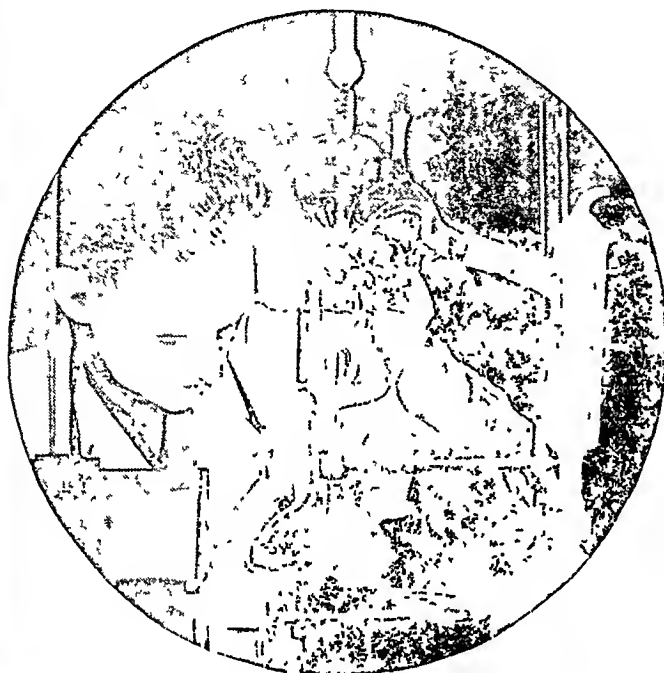
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Merck experience in the production of vitamins extends from the time of the original synthesis of the first pure vitamin, down through the recent isolation of Vitamin B<sub>12</sub> in The Merck Research Laboratories.

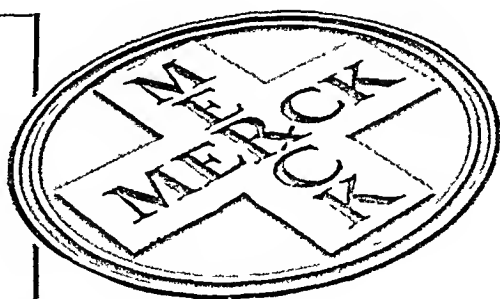
Because most of the known vitamins have now been made available in pure form, effective therapy of specific vitamin deficiencies can be conducted on a rational and controlled basis, under the direction of the physician.

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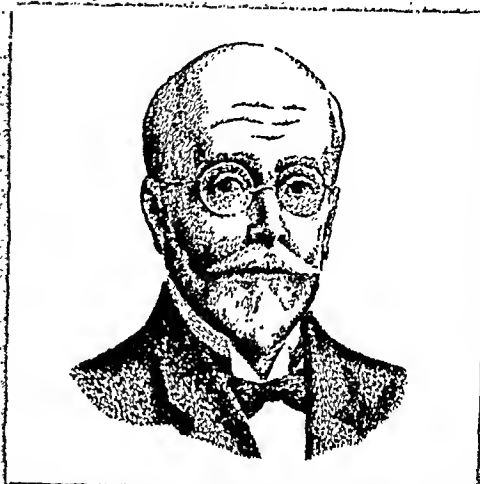
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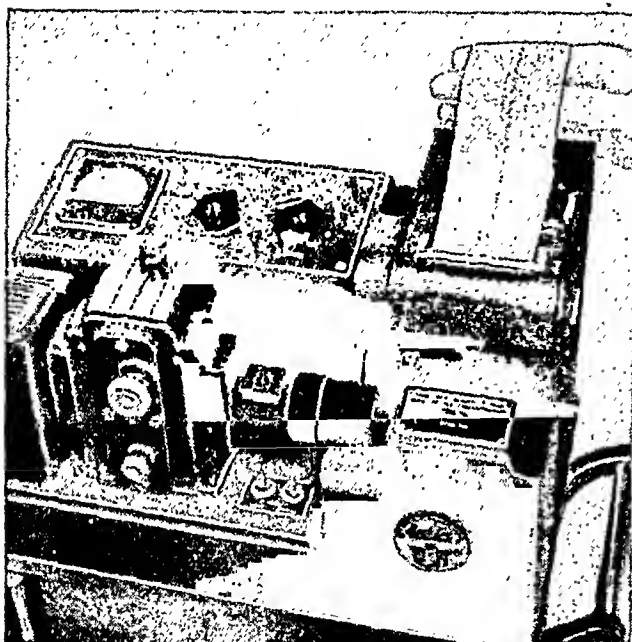
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\*WILHELM F. EINTHOVEN—Physicist, inventor of the quartz string electrocardiograph and Nobel Prize winner for his pioneer work in cardiology.



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Important!—Do not take directly  
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May be thinned with water, milk, or  
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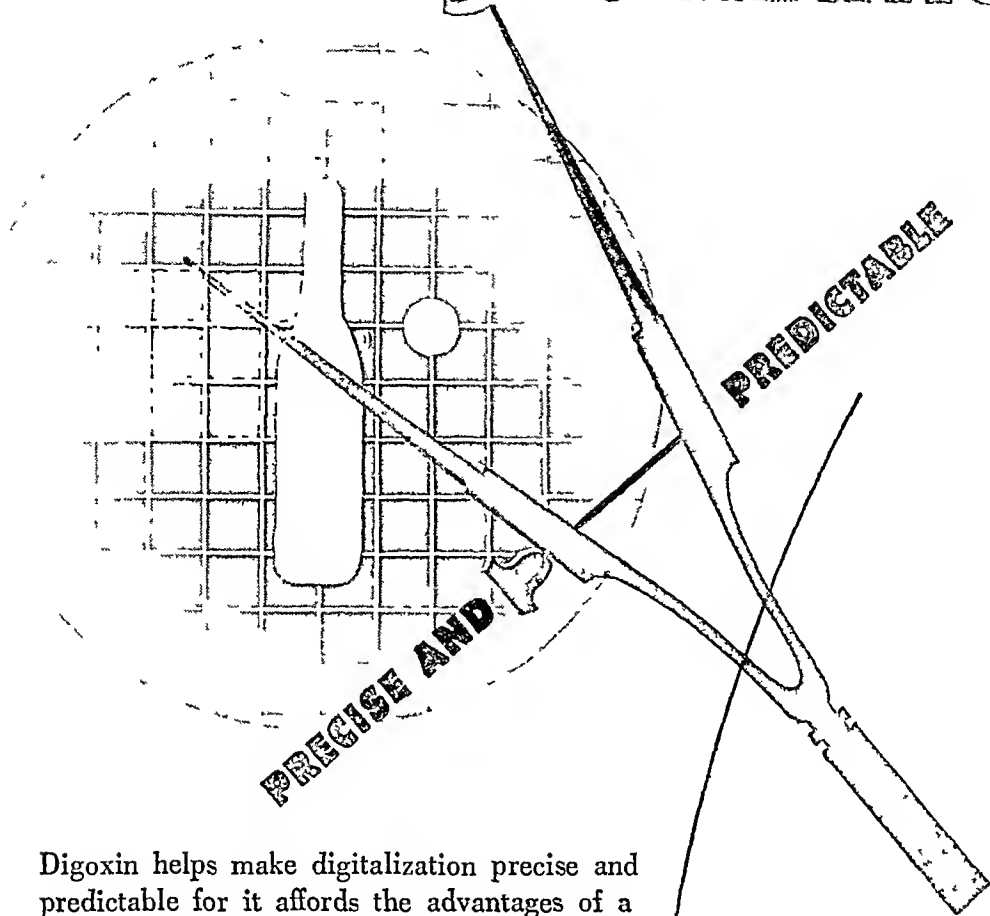
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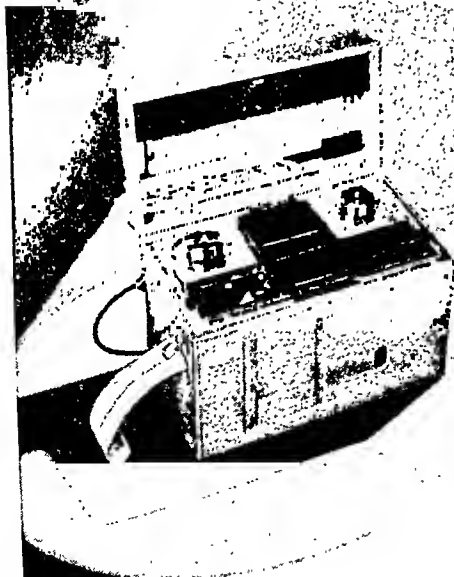
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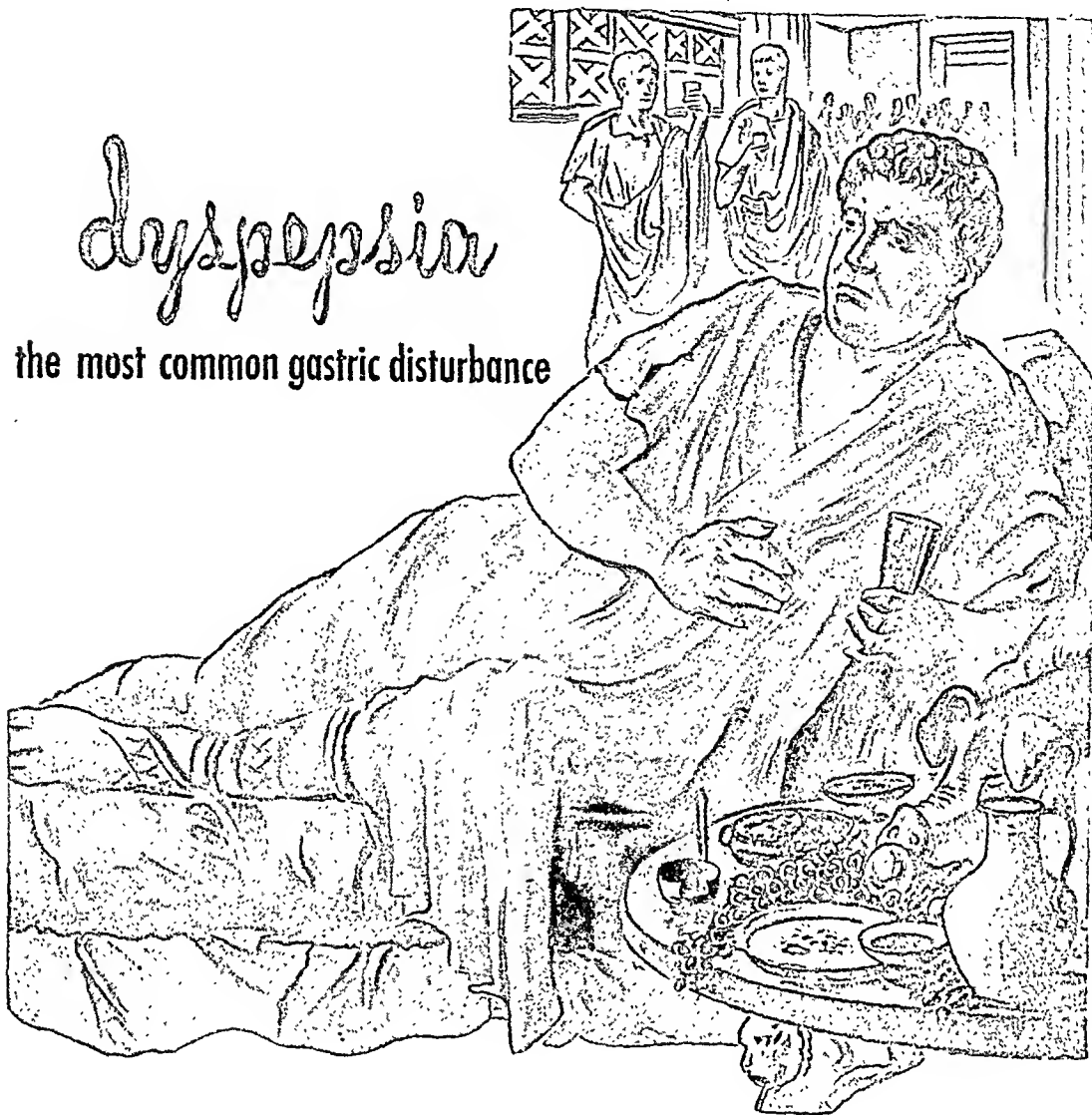
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1. Friedlaender, A. S., Friedlaender, S. (1948), Amer. J. Med. Sc., 215:530, May.
2. Friedlaender, A. S., Friedlaender, S. (1948), Amer. Prac., 2:643, June.
3. Brunsting, L. A. (1948), Canadian Med. Assn. J., 58:133, February.
4. Martins, J. K. (1948), Indust. Med., 17:133, April.
5. Feinberg, S. M., Bernstein, T. B. (1947), J. Lab. & Clin. Med., 32:1370, November.

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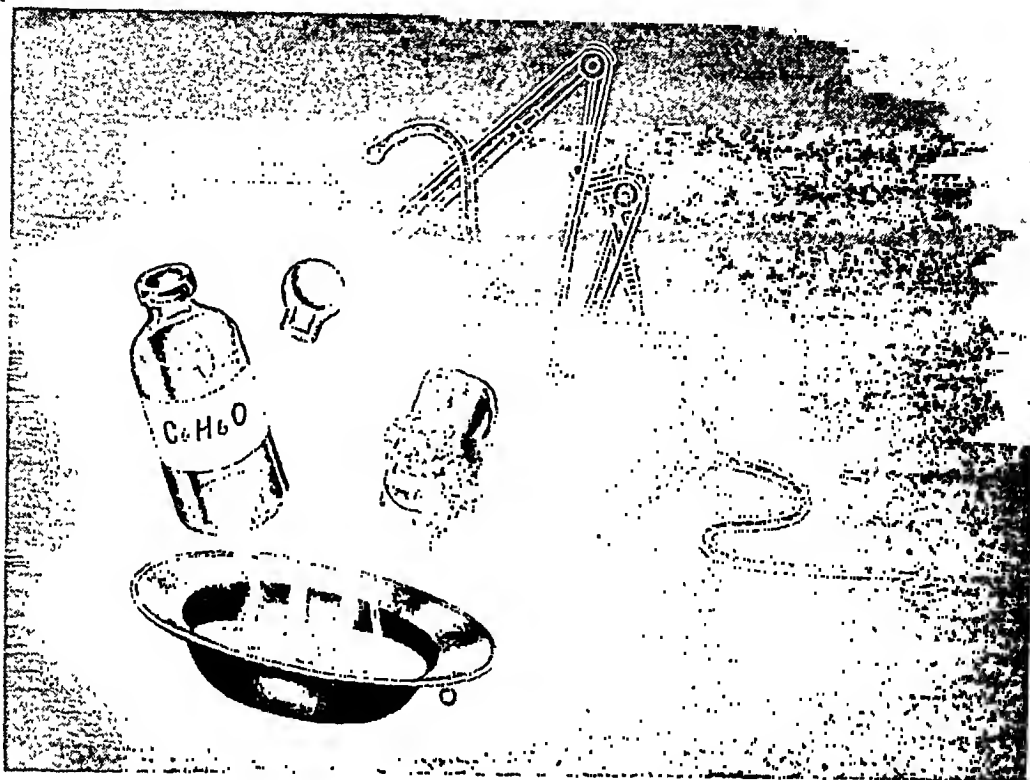
**BIBLIOGRAPHY:** 1. United States Dispensatory, ed. 24, Philadelphia, J. B. Lippincott Company, 1947, p. 1446. 2. Wiesbader, H., and Filler, W.: Am. J. Obst. & Gynec. 51:75, 1946. 3. Allen, W. M.: South. M. J. 37:270, 1944. 4. Lyon, R. A.: Am. J. Obst. & Gynec. 47:532, 1944. 5. Groper, M. J., and Biskind, G. R.: J. Clin. Endocrinol. 2:703, 1942. 6. Soule, S. D.: Am. J. Obst. & Gynec. 45:315, 1943.

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*Medicine and Dentistry* thank Joseph Lister (1827-1912) for discovering the principle of the prevention and cure of sepsis in wounds.

Convinced of a connection between Pasteur's bacteriological discoveries and his own perplexing quest for an answer to wound putrefaction, Lister in 1865 investigated a report that the town of Carlisle was solving its problem of sewage stench with carbolic acid. Returning to Glasgow, he made experiments proving that carbolic—plus clean, sterile hands, ligatures, etc.—effectively curbed surgery's traditional scourge, gangrene.

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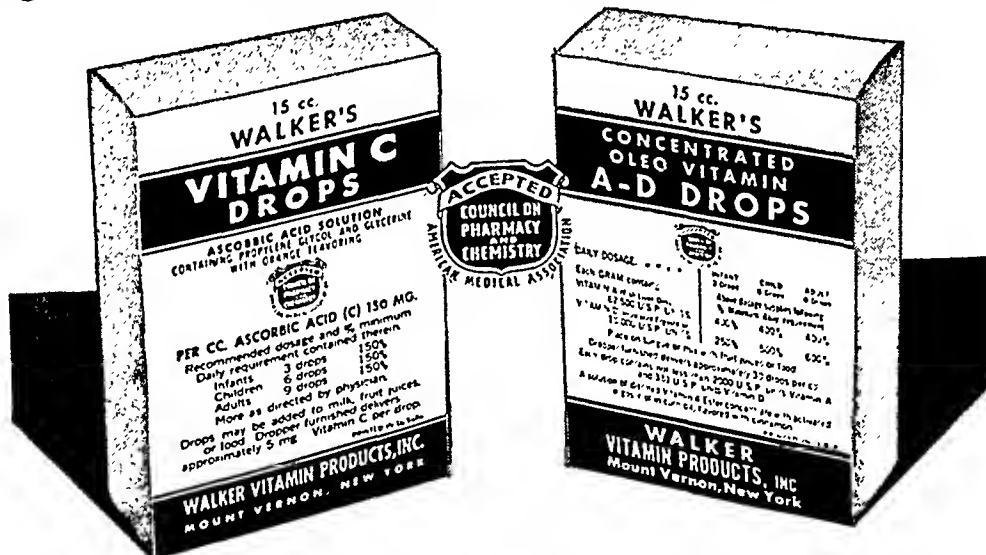
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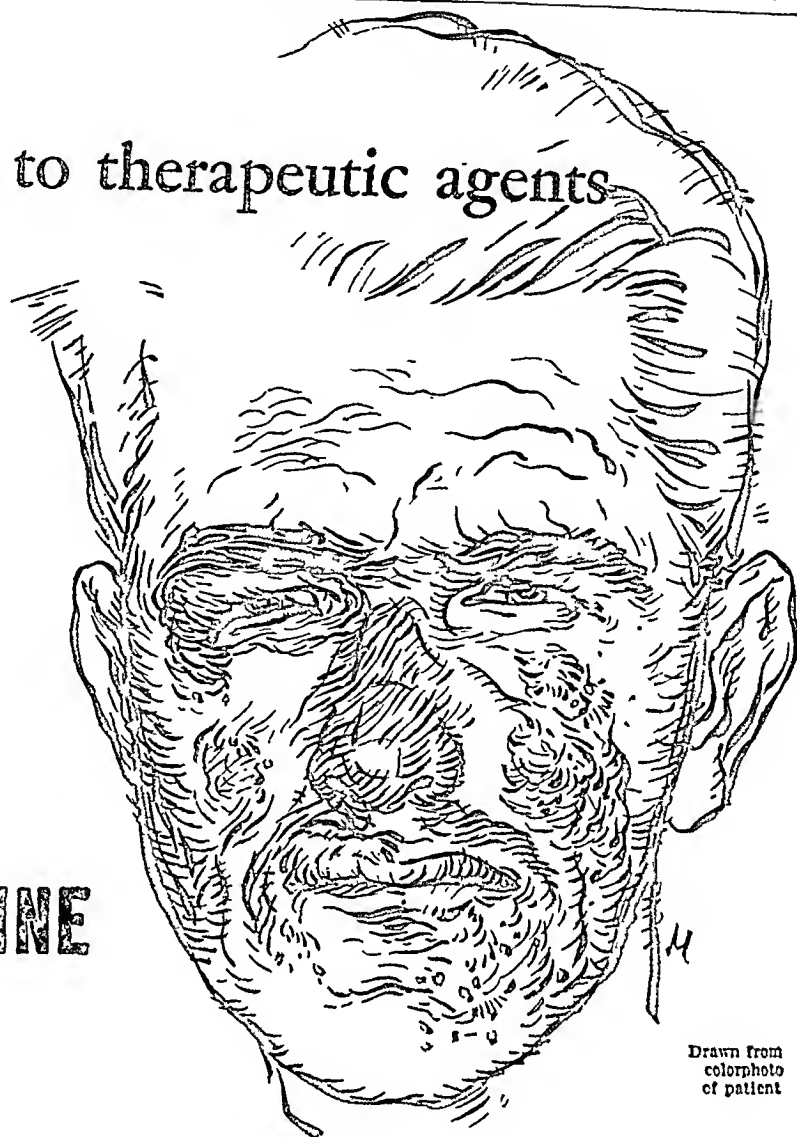
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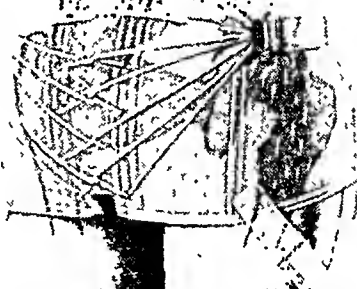
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The dorsal spine curves backward with compression of the dorsal intervertebral discs and the cervical spine curves forward with the articular facets in this region

closer together. Therefore, chronic strain of the muscles, ligaments and joints of the spine and pelvis occurs.

Camp Anatomical Supports have an adjustment by means of which their lower sections can be evenly and accurately brought about the major portion of the bony pelvis. When the pelvis is thus steadied, the patient can contract the abdominal muscles with ease and then with slight movement straighten the upper back.

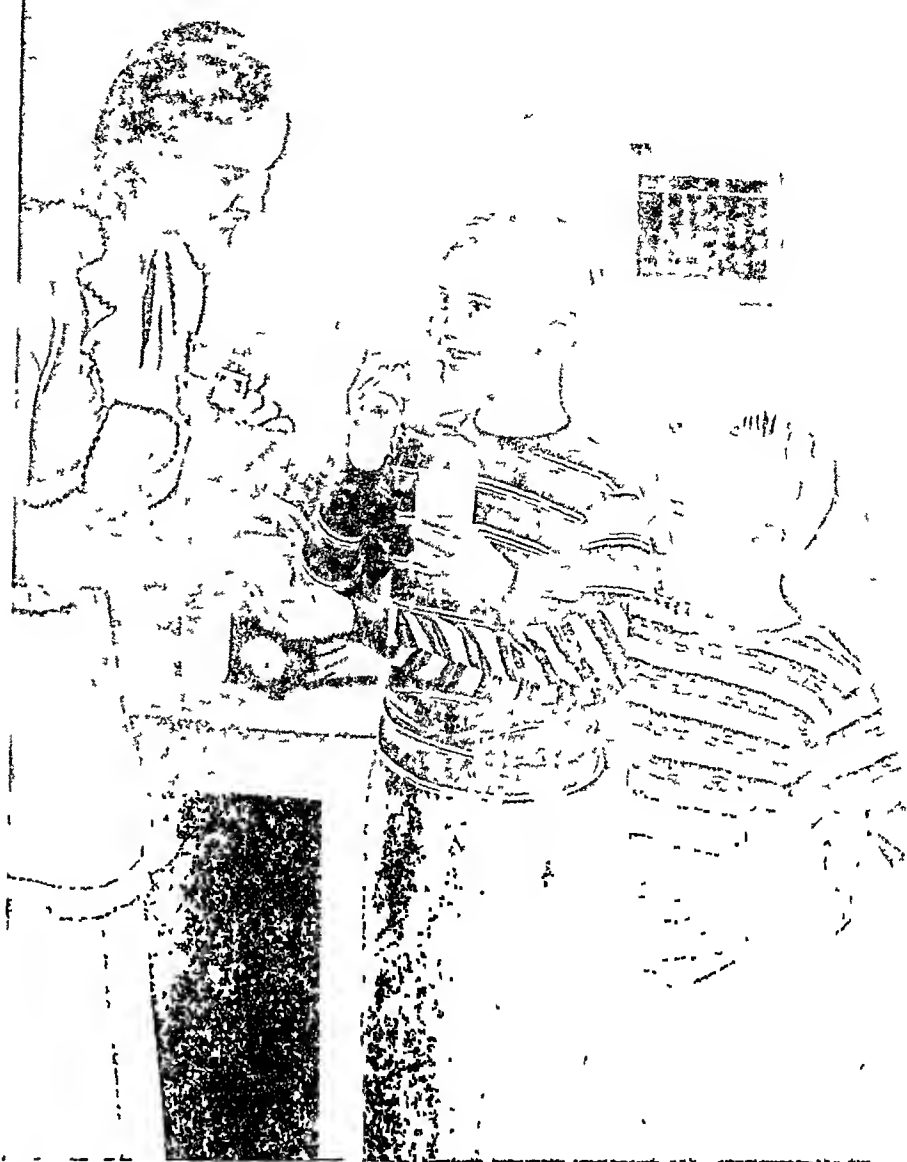
*Relieving back strain and fatigue due to faulty body mechanics is a feature of the Camp Support illustrated and other types for Prenatal, Postnatal, Postoperative, Pendulous Abdomen, Visceroptosis, Nephroptosis, Hernia and Orthopedic conditions.*

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... the natural vitamins A and D—in tablets so remarkably pleasant tasting that children delight in chewing them.

... a well tolerated form—no excess calories, appetite is not affected.

... full potency—each tablet is equivalent, in vitamin content, to one teaspoonful of cod liver oil<sup>1</sup> and supplies 312 units of vitamin D, wholly derived from cod liver oil, and 3,120 units of vitamin A supplied by cod liver oil concentrate adjusted and standardized with fish liver oils.

... an economical preparation—especially suited to maintaining antirachitic protection through the growth years. Also available in "drop-dosage" Liquid for infants and in higher potency capsules.



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There is no better way of satisfying the thirst of the febrile subject than by letting him drink



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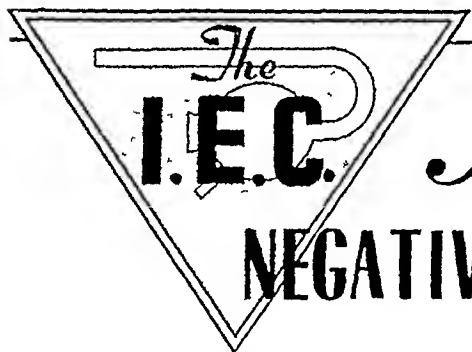
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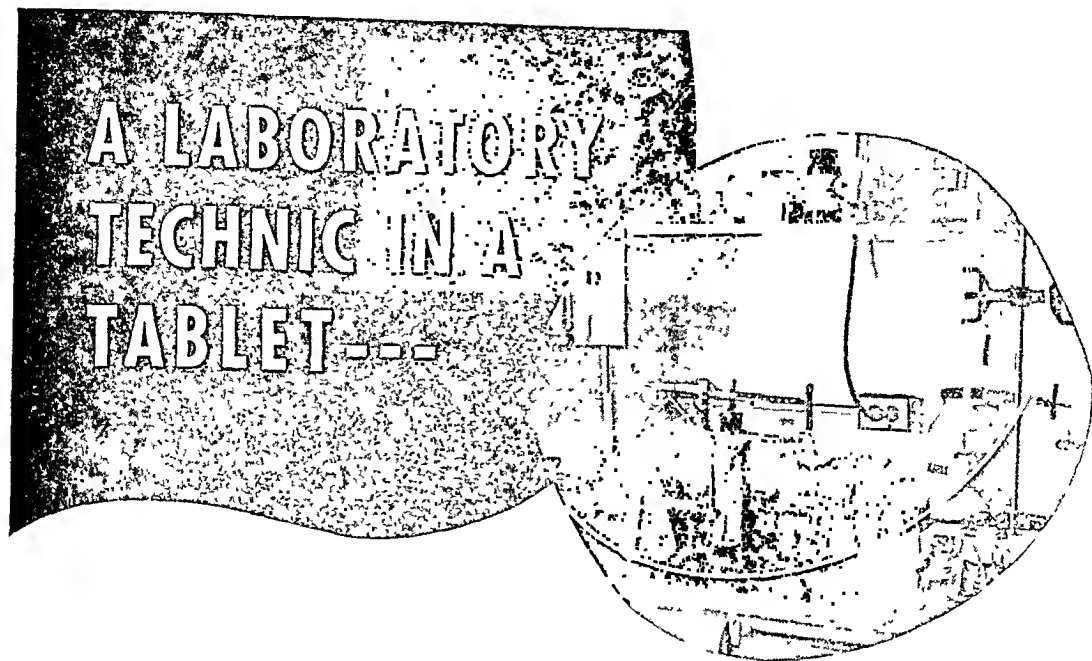
Ref.: A. L. Barach, M.D., M. Soroka, B.S., et al.  
New York State J. Med., vol. 47, No. 13 (July 1947).

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## Metrazol

*intravenously, intramuscularly, subcutaneously*



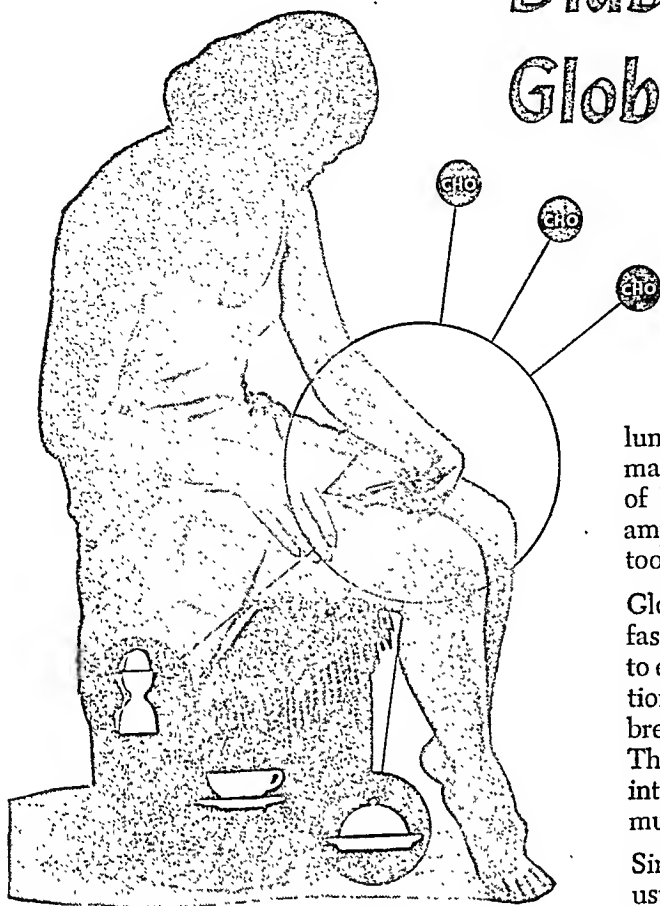
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**SOME FACTS ABOUT DIETARY ADJUSTMENT:** The distribution of carbohydrate in the meals must be adjusted in accord with the type of action exhibited by Globin Insulin, which is intermediate between regular and protamine zinc insulin. Proper carbohydrate distribution with proper insulin timing is essential; lack of balance may lead to poor control or to an erroneous impression of the characteristics of Globin Insulin.

A good carbohydrate distribution for the patient on Globin Insulin is to divide the total carbohydrate per day into 1/5 at breakfast, 2/5 at

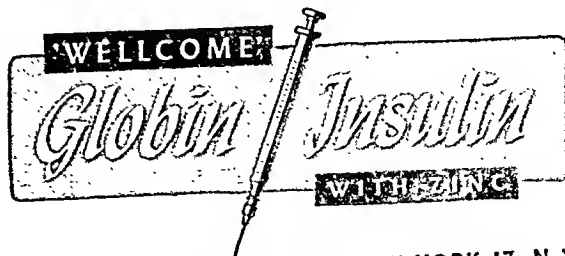
lunch and 2/5 at suppertime. This initial diet may be adjusted in accord with the indications of blood sugar levels and urinalyses. (For example, a low blood sugar before supper indicates too little carbohydrate for lunch or vice versa.)

Globin Insulin is ordinarily given before breakfast. Onset of action is usually sufficiently rapid to eliminate the need for a supplementary injection of regular insulin. However, the amount of breakfast carbohydrate should not be too large. The right amount, as well as the optimal time interval between the injection and breakfast, must of course be determined for each patient.

Since the maximum action of Globin Insulin usually occurs in the afternoon or early evening, hypoglycemia is sometimes noted at this time. As a guard against it, the carbohydrate content of the noon meal may be increased, or a midafternoon lunch provided. Thus the original distribution of 1/5, 2/5 and 2/5 might, for example, require adjustment to 2/10, 5/10 and 3/10 or to 2/10, 4/10, 1/10 and 3/10. Once the balance of carbohydrate intake and insulin timing has been established, the patient must be impressed with the importance of adhering to the regimen.

'Wellcome' Globin Insulin with Zinc is a clear solution, comparable to regular insulin in its freedom from allergenic properties. Available in 40 and 80 units per cc., vials of 10 cc. Accepted by the Council on Pharmacy and Chemistry, American Medical Association. Developed in The Wellcome Research Laboratories, Tuckahoe, New York. U.S. Patent No. 2,161,198. LITERATURE ON REQUEST.

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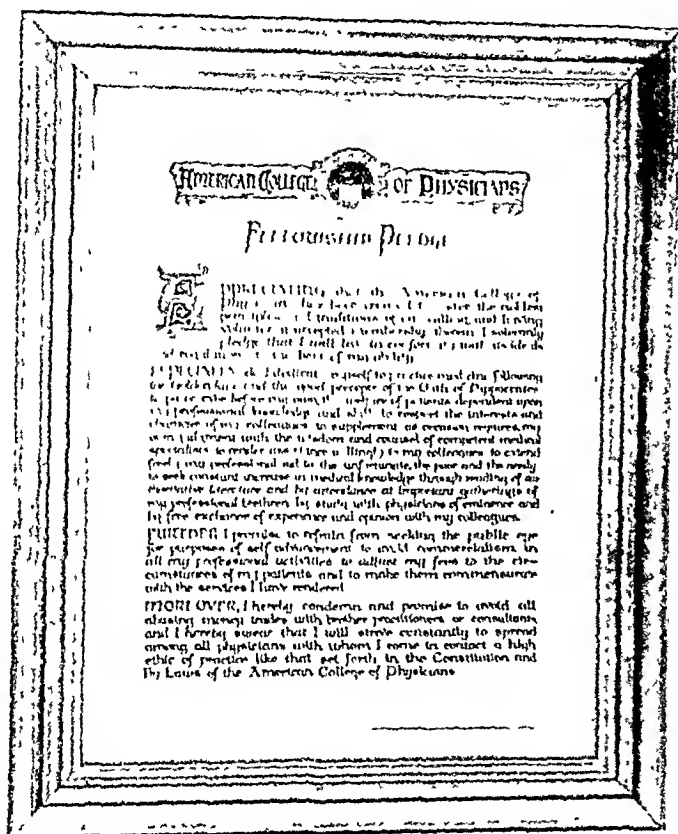


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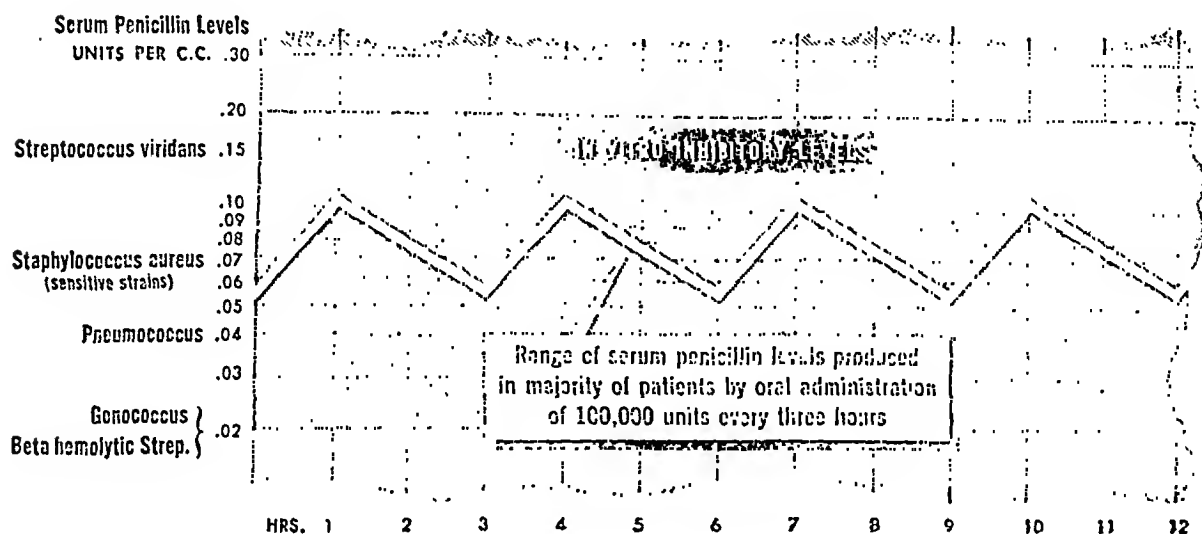
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*"is therapeutically successful even in serious infections, if a sufficiently high dose is given."<sup>1</sup>*



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**POTENT, BUFFERED, INDIVIDUALLY WRAPPED**, hermetically sealed for complete protection against potency-destroying moisture. Tablets of 50,000 and 100,000 units, boxes of 12 and 100. Ref. Hoffman, W. S., and Volini, I. F.: *Am. J. M. Sc.* 213:520 (May) 1947.

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# ANNALS OF INTERNAL MEDICINE

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## BACTERIAL RESISTANCE TO ANTIBIOTICS \*

By C. PHILLIP MILLER, M.D., F.A.C.P., *Chicago, Illinois*

THE development of resistance to the antibiotic drugs is a problem of theoretical interest to the bacteriologist and of practical importance to the clinician.

I should like to describe briefly some experimental studies on the development of bacterial resistance to penicillin and streptomycin and then discuss the clinical implications suggested by these laboratory observations.

### DEVELOPMENT OF PENICILLIN RESISTANCE

Resistance to penicillin can develop in some bacteria, but it usually develops slowly. Meningococcus, for example, has been found to acquire resistance to penicillin if it is repeatedly subcultured onto media containing increasing concentrations of the drug. The graph in figure 1 plots the highest concentration of penicillin on which a strain of meningococcus was able to grow at each subcultivation.<sup>1</sup> Its resistance finally reached a level of 5,000 units per c.c. of media, a 16,600-fold increase, but this increase required 147 transfers.

Development of penicillin resistance has been explained by Demerec<sup>2</sup> as being due to the appearance of penicillin-resistant variants which arise in the bacterial population by the process of mutation. Fortunately, the degree of resistance possessed by any single mutant is but slightly greater than that of the original bacterial population in which it appears.<sup>3</sup> For that reason penicillin-resistance seldom proceeds rapidly.

Increase in resistance can also be produced in vivo. Figure 2 shows the development of resistance which occurred during the course of repeated passage through mice treated with subcurative doses of penicillin.<sup>4</sup> Each point on the graph represents the dose of penicillin which protected approximately 50 per cent of the mice (PD50) at each passage. This was determined at each inoculation by infecting several groups of mice and treating them with

\* Presented at a General Session of the twenty-ninth annual meeting of the American College of Physicians, San Francisco, April 21, 1948.

From the Department of Medicine, University of Chicago.

graded doses of penicillin. The PD50 rose slowly for a time, then rapidly to a level of 1,000 units. Above that level, additional resistance was acquired very slowly. We have no explanation to offer for the shape of this curve.

These experiments demonstrate that a penicillin-sensitive microorganism like meningococcus can acquire resistance both in vitro and in vivo but

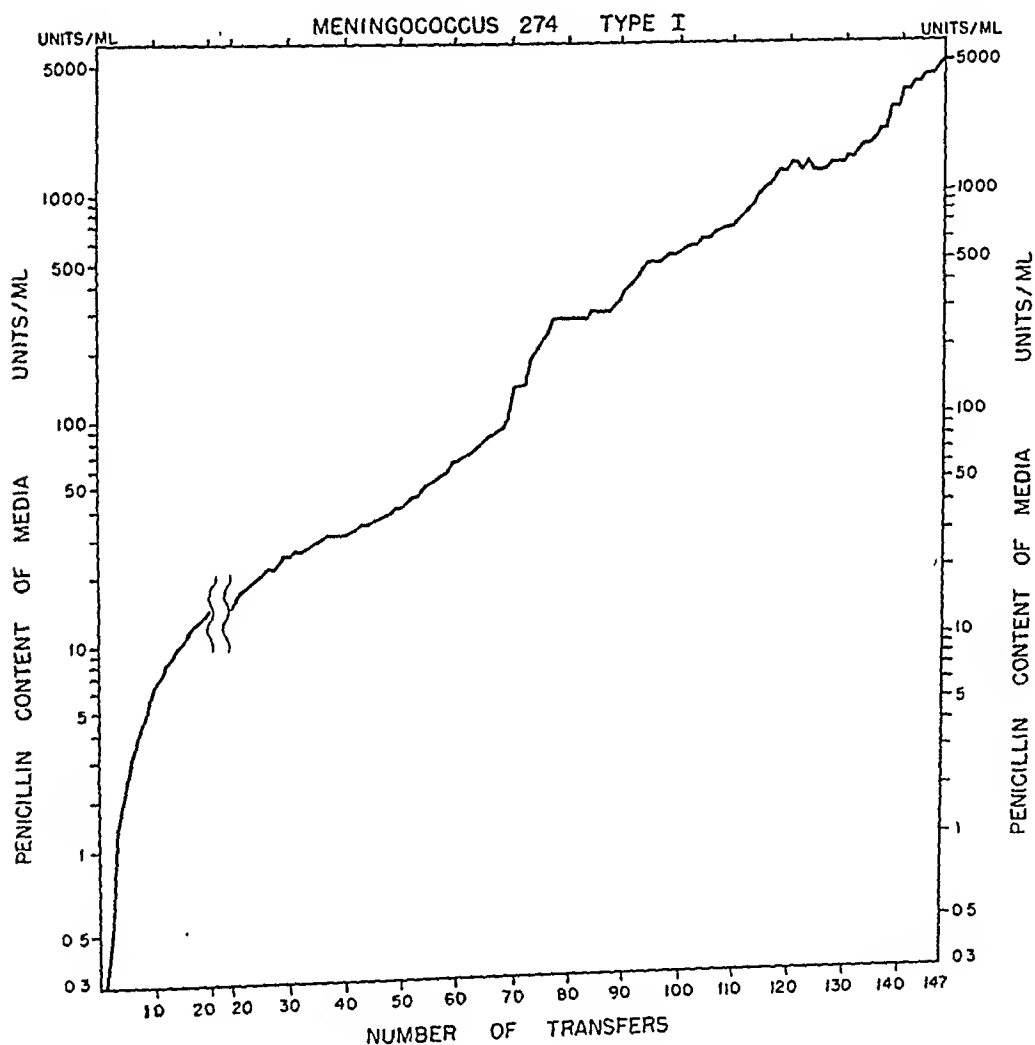


FIG. 1. Development of penicillin resistance by meningococcus during 147 transfers onto media containing increasing concentrations of the drug. The break after the twentieth transfer was occasioned by contamination of the strain which necessitated resumption of the series with a subculture which had been put away in the dry ice refrigerator.

usually at a slow rate even under the most favorable experimental conditions. This is the first of three reasons why resistance to penicillin so seldom becomes a serious practical problem for the physician in his clinical use of the drug. The second is the extraordinary effectiveness of penicillin in combating infection. Most sensitive bacteria are completely eliminated before they have time to develop resistance. The third reason is the cus-

tomary practice of administering penicillin in doses larger than is actually necessary for the control of most infections. Now that penicillin is relatively cheap and the supply abundant, doses are usually prescribed which provide a margin of safety sufficient to take care of some increase in resistance if it should occur. It is doubtful if any infections such as meningococcal meningitis, gonococcal urethritis, or pneumococcal pneumonia have been refractory to treatment because the organism has become resistant to penicillin.

Some strains of bacteria seem never to develop resistance even under

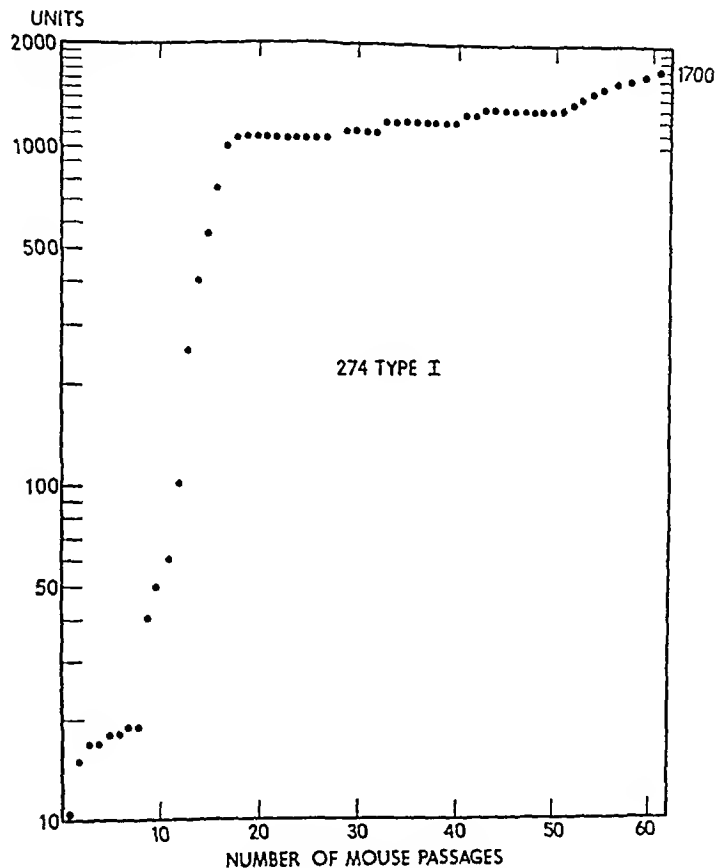


FIG. 2. Development of penicillin resistance by meningococcus in vivo. Dose of penicillin which protected approximately one-half of the mice at each inoculation.

carefully controlled experimental conditions. Gezon<sup>5</sup> has found, for example, that some hemolytic streptococci maintain their original sensitivity to penicillin in spite of prolonged cultivation on penicillin media. Others acquired resistance to such a slight degree as to be negligible from the clinical point of view.

On the other hand, some bacteria readily develop resistance to penicillin in vitro; e.g., staphylococci.<sup>6</sup>

## DISPLACEMENT OF PENICILLIN-SENSITIVE BY PENICILLIN-RESISTANT BACTERIA

The foregoing remarks concern the development of resistance by bacteria originally sensitive to penicillin. This phenomenon must not be confused in clinical observation with the displacement of penicillin-sensitive by penicillin-resistant microorganisms during the course of treatment. Among the staphylococci, for example, some strains are naturally resistant. Most of the highly resistant staphylococci owe this property to their ability to elaborate penicillinase, a substance which inactivates penicillin.<sup>7</sup> These penicillinase-producing staphylococci are rather common and appear not infrequently as secondary invaders in infectious processes, such as wounds, which are exposed to contamination. Indeed, Barber<sup>8</sup> believes that such resistant strains are becoming more prevalent. In making cultures from infected areas care should be exercised to detect the presence of any penicillin-resistant staphylococci which may be present in small numbers. This can be done as Barber recommends by inoculating primary cultures onto media containing a strip of penicillin agar, the original ditch plate or trough plate method described by Fleming.<sup>9</sup>

When one of these highly resistant staphylococci is found after treatment in an open lesion such as a wound from which a sensitive staphylococcus was originally isolated, one is tempted to conclude that the original strain has developed resistance as a result of penicillin therapy. Such a conclusion is not warranted unless one can be quite certain that the possibility of secondary invasion has been ruled out or that the original cultures were not contaminated by small numbers of resistant bacteria which might have been overlooked. One must, therefore, be cautious about ascribing failure of cure to the development of resistance to penicillin unless one can be sure that an infection is being maintained by the same strain which initiated it.

## DEVELOPMENT OF STREPTOMYCIN RESISTANCE

In sharp contrast with the slow rate at which bacteria develop resistance to penicillin is their behavior toward streptomycin to which they can acquire a very high degree of resistance in a very short time.<sup>10</sup> Two or three transfers onto streptomycin media suffice to permit sensitive bacteria to grow abundantly on concentrations as high as 50,000 micrograms per c.c. This extraordinary increase in streptomycin resistance is due to the appearance of streptomycin-resistant variants which arise by mutation in a normal bacterial population.<sup>11, 12</sup> These mutants, unlike the penicillin-resistant mutants, are able to grow on high concentrations of streptomycin. They are also remarkable in that they consist of two types, both of which are resistant to streptomycin, but one of which can multiply only on streptomycin-containing media; that is, it is dependent on streptomycin for its growth.\*

\* This investigation was supported jointly by the U. S. Navy, Office of Naval Research, and the University of Chicago.

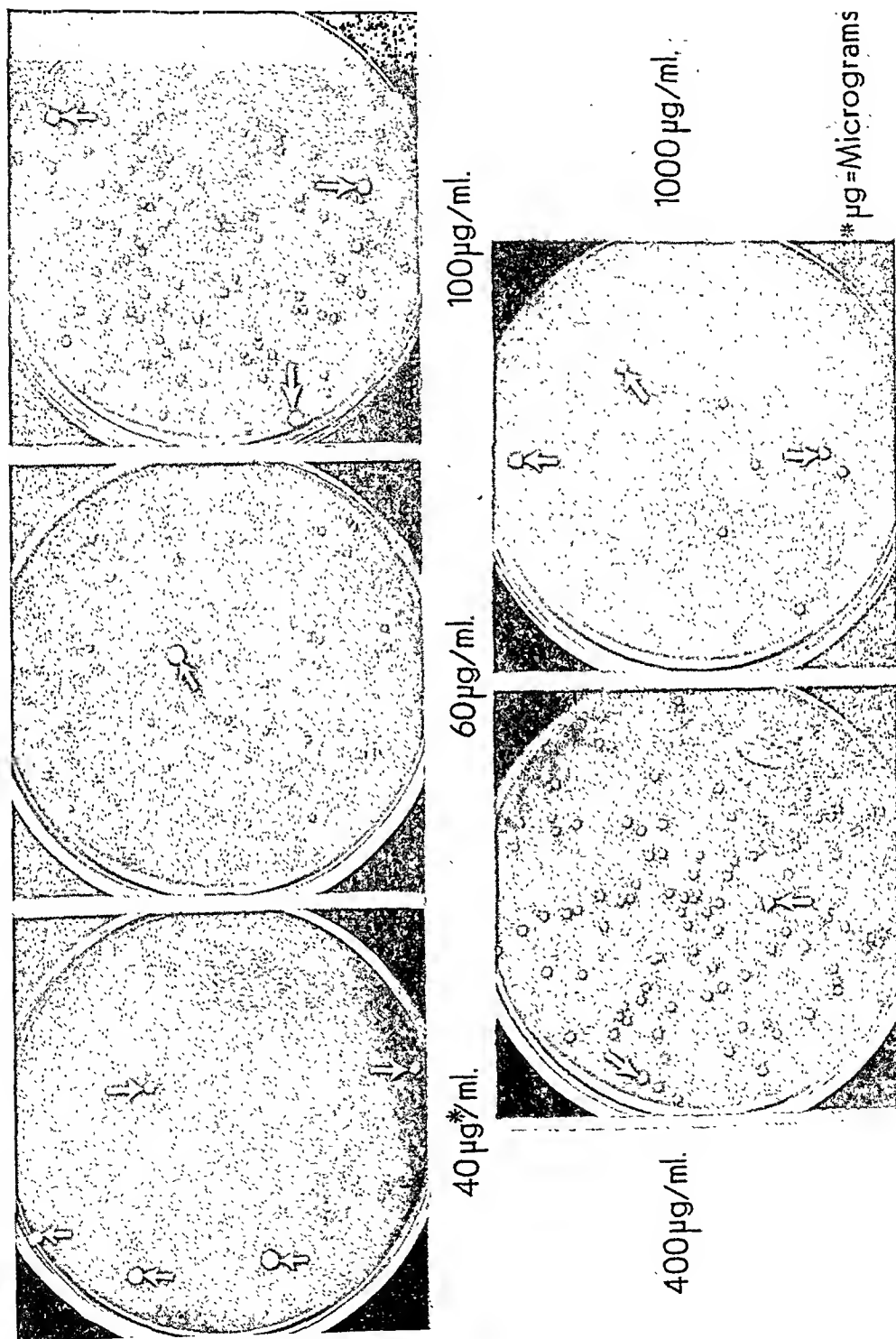


FIG. 3. Growth of meningococcus from equivalent inocula on graded concentrations of streptomycin 72 hrs. incubation.

Both types are easily demonstrable when heavy seedings of an organism like meningococcus are planted onto a series of plates containing graded concentrations of streptomycin as shown in figure 3. It should be borne in mind that the plates were inoculated simultaneously with approximately equal numbers of sensitive meningococci which had never been exposed to streptomycin.

Colonies of 2 different types appear on concentrations above 40 micrograms per c.c. One type of colony, designated type A, appears in small numbers on all concentrations. These colonies of meningococcus are highly resistant to streptomycin because they can be subcultured onto any concentration up to 50,000 micrograms per c.c. They will also grow on streptomycin-free media. They are virulent for mice, producing infections against which large doses of streptomycin afford no protection.

### STREPTOMYCIN-DEPENDENT VARIANTS

The other type of colony, designated type B, always appears in greatest numbers on concentrations between 100 and 400 micrograms per c.c. These are streptomycin-dependent variants for they cannot be subcultured onto

TABLE I

Growth of Type B (Streptomycin-Dependent) Variants of Meningococcus in Broth

Concentration of Streptomycin	Growth
0 (Control)	0
10 micrograms/c.c.	±
40 micrograms/c.c.	+++
100 micrograms/c.c.	++++
400 micrograms/c.c.	++++
1000 micrograms/c.c.	+++
4000 micrograms/c.c.	±

media containing less than 5 micrograms per c.c. In other words, streptomycin has become a necessary growth factor for these organisms. Although the type B colonies appear in greatest numbers in this optimum concentration, they grow larger in size on higher concentrations. The increase in size seems to be due to a direct, stimulating action of streptomycin and is independent of the rate of establishment of colonies. When a large colony growing on media containing a high concentration is subcultured onto a lower concentration, it develops as small colonies, and conversely when a small colony growing on a low concentration is transplanted onto a high concentration it develops as large colonies. This fact indicates that all of these type B colonies are composed of identical organisms; i.e. they are genetically alike.

Their dependence on streptomycin in broth culture is shown in table 1. Growth occurred only in tubes containing streptomycin and was maximal in concentrations of 100 and 400 micrograms per c.c.

Dependent organisms do not differ (in morphology, sugar fermentations and type specificity) from normal meningococci except that they require streptomycin for their multiplication.

No substance has been found which will substitute for streptomycin in supporting growth of the dependent organisms, although we have tried a number of streptomycin derivatives; e.g., streptamine, streptidine, streptobiosamine and streptomycin which has been inactivated by cystein HCl and hydroxylamine HCl.

#### EXPERIMENTAL INFECTION WITH STREPTOMYCIN-DEPENDENT BACTERIA

The dependence of these organisms on streptomycin is demonstrable in vivo as well as in vitro. When inoculated into mice, they are unable to produce infection unless the animals are treated with streptomycin. Table 2 presents the results of a typical experiment. Three groups of mice were infected with different inocula of streptomycin-dependent meningococci. The second and third groups were treated with the drug and the first group served as untreated controls. The control mice, although inoculated with much larger numbers of meningococci, all survived, but those mice which were treated with streptomycin all died.

TABLE II

Results of Streptomycin Treatment of Mice Infected with Type B (Streptomycin Dependent) Variants of Meningococcus

Number of Meningococci Inoculated	Streptomycin Treatment	No. Mice	Result	Heart's Blood Cultures
10,000,000	No treatment	6	All survived	
100,000	10,000 $\mu$ gm. (in 4 doses) during first 12 hrs. of infection	12	All died	{Positive on streptomycin media    {Negative on streptomycin-free media
10,000		8	All died	

The heart's blood of each was cultured in duplicate onto streptomycin-containing and streptomycin-free media. All of the heart's blood cultures were positive on streptomycin media and negative on streptomycin-free media.

This experiment brings out 2 points: first, that these variants require streptomycin for multiplication in vivo as well as in vitro, and second that they retain their dependence on streptomycin after they have passed through the body of an infected animal host.

This is not a chance observation for it has been repeated many times. Nor is the demonstration of streptomycin-dependent variants an isolated finding. They, as well as type A variants have been recovered from all of 18 strains of meningococcus including types I, II and II alpha and from a number of other bacterial species, including *Escherichia coli*, several strains of *Salmonella*, *Aerobacter aerogenes*, *Proteus vulgaris*, *Pseudomonas pyocyanea*, *Staphylococcus albus* and *aureus* and alpha hemolytic streptococcus. These findings have been confirmed by Paine and Finland,<sup>13</sup> by Kushnick and his co-workers,<sup>14</sup> by Yegian and Budd<sup>15</sup> and by Rake.<sup>16</sup>



The fact that both types of variants have been recovered from a number of bacterial species indicates that this is a general phenomenon and is not restricted to any one group of microorganisms.

Certain metabolic peculiarities of these streptomycin-dependent variants are now being examined in the hope of obtaining an insight into the mechanism of action of streptomycin.

#### THE OCCURRENCE OF STREPTOMYCIN-RESISTANT AND STREPTOMYCIN-DEPENDENT BACTERIA IN ANIMALS AND MAN

The question naturally arises whether these streptomycin-dependent variants occur in nature or whether they develop only in vitro under the artificial conditions of laboratory experimentation.

This possibility has been investigated by treating normal rabbits and mice with large doses of streptomycin and making periodic cultures of the pharynx and large bowel. The cultures were made on media containing 400 micrograms of streptomycin per c.c. After a week both type A and type B variants were recovered from these animals.

We also made throat cultures on patients\* who were being treated with streptomycin. It was found that streptomycin-resistant bacteria, including a small proportion of streptomycin-dependent bacteria, could be recovered from throats of those who had received 1 gram or more of streptomycin a day for more than two weeks.<sup>17</sup> Control cultures were made of the throats of patients who were not receiving streptomycin and of members of the hospital staff, students, and laboratory personnel and ward personnel. The cultures were all made by the author. The posterior pharyngeal wall was swabbed in the ordinary way and inoculated onto two agar plates containing 200 and 400 micrograms of streptomycin per c.c. Only streptomycin-resistant and streptomycin-dependent organisms were able to grow on these concentrations of streptomycin. With few exceptions, the bacteria which were isolated belonged to the ordinary species found in the flora of normal throats and were in no way related to the infections for which streptomycin was being administered.

Table 3 shows the results of these throat cultures. Ninety-eight per cent of the streptomycin-treated patients had positive cultures. These cultures were all positive by the thirteenth day of treatment. The 10 per cent of positive cultures from patients who were not receiving streptomycin contained relatively few organisms. Among 157 members of the staff, medical students and laboratory personnel, 4 per cent had a few resistant microorganisms on their plates. The highest incidence of positive cultures in our control group, 21 per cent, occurred among the nurses and maids working on the wards. All the strongly positive cultures came from nurses who were caring for patients receiving streptomycin. This series is too small to be significant, but it does suggest that streptomycin-resistant organisms which

\* In the Albert Merritt Billings Hospital, University of Chicago Clinics.

develop in the throats of treated patients may be transferred to the nurses who look after them.

The organisms recovered on these cultures were all streptomycin-resistant. They were predominantly type A (resistant) organisms but a certain proportion were streptomycin-dependent (type B). These results together with those in the animal experiments mentioned earlier seem to settle the question whether streptomycin-dependent bacteria occur outside of the laboratory.

The microorganisms isolated from these cultures were the ordinary bacteria found in the normal human pharynx—staphylococci, streptococci, diphtheroids, *Neisseriae*, *M. tetragenus*—except that they included a higher proportion of yeast-like forms than is usually encountered. There was no evidence that any of these microorganisms was pathogenic.

Cultures on a second series of patients treated with small doses of streptomycin in a tuberculosis sanatorium \* suggest that streptomycin-resistant bacteria appear more slowly in the throats of patients receiving only 0.5 gram a day.

TABLE III  
Results of Throat Cultures on Media Containing Streptomycin

Source of Culture	Number of Individuals	Result			Per Cent Positive
		Negative	Positive		
			Few Colonies <25	Heavy Growth >25 Colonies	
Streptomycin-treated patients	59	1	5	53	98%
Untreated patients	70	63	4	3	10%
Ward personnel	99	78	7	14	21%
Staff, students and laboratory per- sonnel	157	150	6	1	4%

### SUMMARY

Resistance to penicillin can be developed by bacteria in vitro and in vivo but it proceeds relatively slowly. Resistance to streptomycin, on the other hand, can develop rapidly owing to the appearance of streptomycin-resistant variants which arise in a bacterial population by the process of mutation. These mutants are of two types, both of which are resistant and one of which is dependent on streptomycin for its growth in vitro and in vivo. Both types can arise among the normal microbial inhabitants of the upper respiratory passage of animals and patients during treatment with streptomycin.

\* The Chicago Municipal Tuberculosis Sanitarium, Dr. George C. Turner, Superintendent, to whom the author is indebted for the opportunity to make these cultures.

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# HEREDITARY HEMORRHAGIC TELANGIECTASES ASSOCIATED WITH PULMONARY ARTERIO- VENOUS FISTULA IN TWO MEMBERS OF A FAMILY \*

By JOHN H. MOYER, Captain, M.C., and ALFRED J. ACKERMAN,  
Lieutenant Colonel, M.C., *Fort Sam Houston, Texas*

ALTHOUGH it is generally known that hereditary hemorrhagic telangiectases frequently involve visceral organs, the "cavernous hemangioma" of the lung is so rarely thought of that it usually remains unrecognized, even in the presence of mucocutaneous telangiectases. The clinical symptoms and signs which form the classical manifestations of this disorder are not infrequently attributed to congenital heart disease. Pulmonary opacities demonstrated radiologically have been usually misinterpreted, though they may be sufficiently characteristic to permit a correct early diagnosis.

In this presentation it is our intention to discuss the clinicopathological and radiologic manifestations of pulmonary arteriovenous fistulae observed in two members of a family suffering from hereditary hemorrhagic telangiectases. In one of these cases a cure was obtained after pneumonectomy.

## CASE REPORTS

The family, which we are about to discuss, consists of the mother, two daughters and four sons all of whom are living. The father died at age 59 apparently of a pulmonary embolus secondary to phlebothrombosis of the leg. He was well until 20 years of age, when he first noted numerous telangiectases of the face and lips. The facial lesions were photosensitive, resulting in recurrent rupture of the vessels and bleeding on a direct exposure to sunlight. The lesions increased in number and severity until death. He also suffered from numerous attacks of epistaxis, frequently resulting in considerable loss of blood. About two weeks prior to his last hospitalization he ruptured a vessel in one leg while lifting a heavy weight. This was followed by a phlebothrombosis and a pulmonary embolus. His parents were apparently free from the disease.

The mother, 48 years of age, and two daughters, 22 and 19 years old, had several small cutaneous hemangiomata of the face and chest. These siblings exhibited also early small telangiectases of the lips, and the older daughter suffered in the past from recurrent epistaxis.

One son, 25 years of age, had similar early cutaneous and mucocutaneous telangiectases, a red cell count of 6.01 million with 16.5 grams of hemoglobin, and a hematocrit of 53 per cent. The reason for the polycythemia was not apparent, but it may have been indicative of an already existing, not yet demonstrable, congenital arteriovenous fistula of the lung.

The second son, 31 years of age, complained of frequent epistaxis. He first noted telangiectases on the face and lips at the age of 24. Shortly thereafter similar lesions appeared on the mucous membranes of the mouth, tongue and lips. They

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From the Brooke General Hospital, Brooke Army Medical Center, Fort Sam Houston, Texas.

have been increasing in number and have bled frequently. The hemorrhages were more severe following prolonged exposure to direct sunlight.

Physical examination disclosed numerous spider telangiectases over both malar prominences, on both lips, on the tongue, nasal septum and vestibule of the nose. There were several small subcuticular hemorrhages on the exposed part of the upper lip, which had a raised, blue appearance. Several small hemangiomata were scattered



FIG. 1. *Case 1.* Multiple telangiectases of the face and the mucocutaneous junction of both lips.

over the upper chest and both arms. No other abnormalities were observed. Laboratory studies showed a normal blood count and hemoglobin.

The third son (case 1), a sergeant in the Regular Army, developed numerous telangiectatic spots and "blood blisters" involving the face and lips, about seven years ago. He has suffered from severe recurrent epistaxis which caused a significant loss of blood each time. Eight years ago, following heavy lifting, he had spontaneous hematuria with grossly bloody urine which lasted several days.

Physical examination revealed a well developed, well nourished robust male. There were numerous spider nevi over both malar prominences, and numerous small telangiectases on the lips, tongue and right vestibule of the nose, varying in size from pin-head to 0.25 centimeter. There were also numerous subcuticular hemorrhages on the lips. Three small hemangiomas were present on the chest. Examination of the chest and heart was negative, except for an accentuated aortic second sound, which was transmitted to the axilla. The tourniquet test was negative and fundoscopic examination of the retina revealed no hemorrhages or vascular abnormalities.



FIG. 2. Case 2. Multiple telangiectases of the face and the mucocutaneous junction of the lower lip.

Radiologic examination of the chest revealed a round area of increased density in the left lung field at the level of the fourth rib anteriorly measuring 2 centimeters in diameter. There was a vessel leading from the left pulmonary artery to this area. These findings were thought to be consistent with a small arteriovenous fistula. Angiography revealed dye within the previously described round opacity. Two vascular bands connected this opacity with the hilar vessels. The superior band was rather tortuous and of slightly greater width. On intravenous urography the collecting systems of both kidneys were well visualized by the dye. The superior lateral margin of the right renal pelvis was slightly concave. The upper calyx was possibly compressed near its junction with the pelvis. There was no other evidence of abnor-

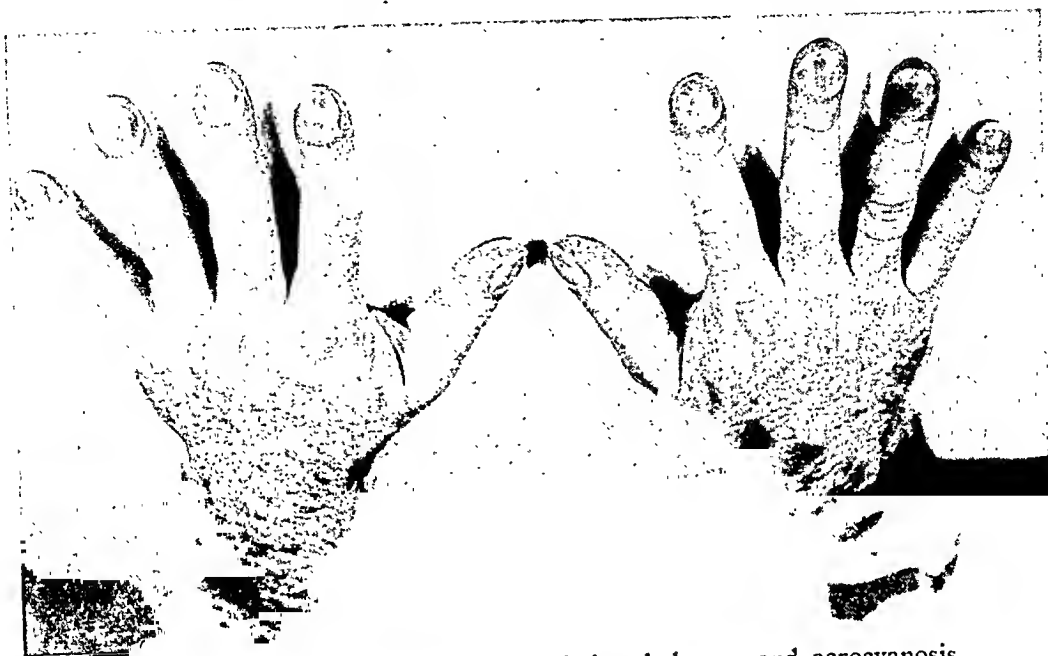


FIG. 3. *Case 2.* Marked clubbing of the phalanges and acrocyanosis.

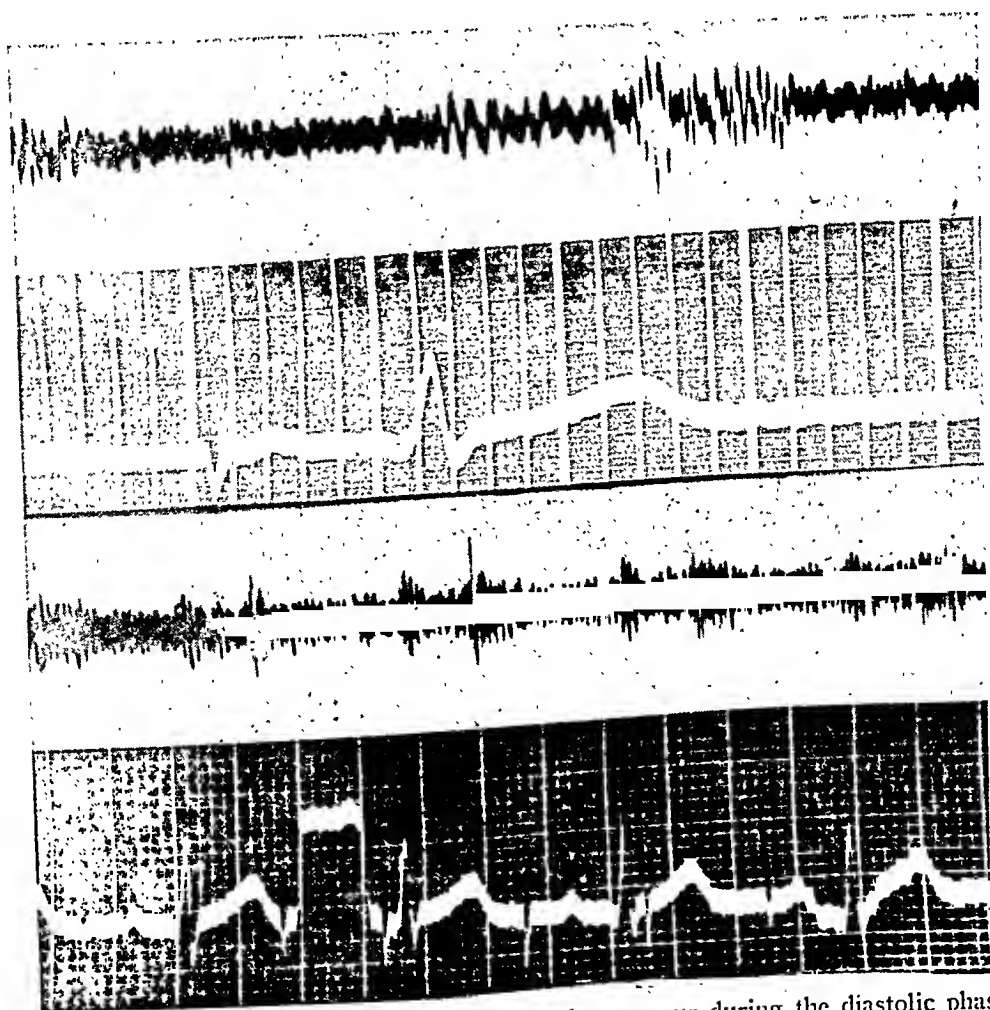


FIG. 4. *Case 2.* Stethogram demonstrating the murmur during the diastolic phase of the cardiac cycle.

malitiy. In view of the history of so-called "essential hematuria" these findings suggested the possibility of a hemangioma within the kidney. Laboratory studies revealed a red cell count of 4.8 million; a white cell count of 10,000; 15.5 grams of hemoglobin; a hematocrit of 44 per cent; a differential of 64 per cent polymorphonuclears, 32 per cent lymphocytes, 2 per cent eosinophiles, 2 per cent monocytes; a blood volume of 9,300 c.c. determined by the Congo red method; a plasma volume of 64 c.c./1 kg; a cell volume of 50 c.c./1 kg; and an icteric index of 4.



FIG. 5 Case 1. PA roentgenogram showing a small round opacity at the level of the fourth rib anteriorly.





FIG. 6. *Case 1.* Left lateral roentgenogram: the opacity lies anteriorly and appears to be connected with an abnormal pulmonary vessel.

The fourth son (*case 2*), 26 years old, was admitted to the hospital complaining of attacks of dizziness lasting two to three days. The patient was in good health until 1936, when he had pneumonia, followed by persistent cyanosis. In 1941 he was admitted to an army hospital, complaining of generalized malaise and a moderately severe upper respiratory infection. He had a cough which was productive of a small amount of mucopurulent sputum. The infection subsided within a few days. About a week after hospitalization he developed phlebothrombosis of the right saphenous vein,

which, however, subsided after six or seven days without therapy and without complication. This was followed by episodes of blurred vision, dizziness, weakness and vertigo, not associated with nausea, or vomiting, and lasting only five to ten minutes. The complaints were relieved when the patient was in a prone position and were more severe in an upright position. The episodes recurred approximately every two to three weeks during his original two months of hospitalization. Roentgenograms of the chest revealed a round mass measuring 5 cm. in diameter lying against the

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FIG. 7. *Case 1.* Angiogram: the arteriovenous fistula and its communicating vessels are visualized.

posterior chest wall. It was thought to be localized in the lower portion of the posterior mediastinum, and a presumptive diagnosis of neurofibroma was made. Laboratory studies revealed: red cell count of 8.9 million; hemoglobin 125 per cent; white cell count of 10,450 with 75 per cent neutrophils; 23 per cent lymphocytes; and 2 per cent monocytes. A Schilling count showed 42 per cent segmented forms; 31 per cent band forms; 15 per cent large lymphocytes; 8 per cent small lymphocytes; and 2 per cent metamyelocytes. The urine was normal. Repeated blood studies showed a red cell count of 9.6 million; a white cell count of 3,500 with 638,800 platelets; and a normal differential count.

He was separated from the Service in April, 1941, with a diagnosis of (1) polycythemia, chronic, severe, cause undetermined, and (2) thrombosis, simple, great saphenous vein, right, cause undetermined. He continued to complain of dizziness, weakness, and blurred vision which became sufficiently severe to cause marked diplopia. Between attacks he was entirely asymptomatic except for exertional dyspnea. Immediately following separation from the Army, the above mentioned symptoms occurred only every two to three weeks and lasted for several minutes to several hours. Recently, they have become more severe, confining the patient to bed. The attacks seem to be precipitated by exertion or hot weather. About three years ago (1943) the patient first noted that he had developed clubbing of the fingers and multiple spider telangiectases on the lips, face, and over the bridge of the nose. He also had several moderately severe attacks of epistaxis and observed that on exposure to direct sunlight the telangiectases of the lips frequently ruptured and bled.

Physical examination revealed a well developed, well nourished male, with generalized cyanosis, especially marked on the lips, tongue and fingernails. There was marked clubbing of the fingers and toes. Numerous spider telangiectases were present over the malar prominences and on the upper and lower lips and mucous membranes of the tongue and buccal mucosa. Accompanying these telangiectases were several areas of subcuticular hemorrhage, especially on the lips. The eyes showed marked conjunctival injection with several areas of subconjunctival hemorrhage. The eyegrounds were normal. Pharyngeal mucous membranes were normal except for a dusky hue. The neck veins were markedly distended. There were marked pulsations of the carotid arteries, noted especially in the supra-sternal notch. No murmurs were heard over the neck vessels and the thyroid was not enlarged. Both lungs were apparently normal. The blood pressure was 130 systolic; 80 diastolic. The pulse rate was 80 and of regular rhythm. A marked precordial thrust was noted in the fifth interspace in the mid-clavicular line not associated with any thrill or systolic murmur. A diastolic murmur was audible over the second left costal interspace, transmitted to the third interspace. There was also a blowing murmur in the paravertebral region near the angle of the right scapula over an area about the size of the palm of the hand. This was very pronounced during inspiration and barely audible during expiration. The phase of the cardiac cycle during which the murmur was heard was confirmed by a stethogram which showed a murmur extending through the early and mid-diastolic phases. The abdomen revealed no abnormalities. The liver and spleen were not palpable. All other systems were apparently normal.

Radiologic examination of the chest revealed a circular shadow of increased density in the right lower lung field, which lay near the apex of the right lower lobe. The infero-lateral margin of this density showed a bi-convex contour. On fluoroscopy a slight pulsation of the pulmonary opacity could be seen, and the oblique and lateral views showed a large vessel extending from the hilum and merging with the described shadow. The Valsalva test showed a slight decrease in size of the opacity, and the Mueller test showed an increase in size. Visualization of the heart and great vessels by 50 c.c. of 70 per cent Diodrast demonstrated the dye within the mass.

TABLE I  
Hematological Determinations

Preoperatively			Postoperatively		
Date	Examinations	Values	Date	Examinations	Values
Feb. 26, 1947	Red cell count	8.2 million	Mar. 9, 1947	Red cell count	6 million
	White cell count	5,500		Hemoglobin	17 gm. %
	Differential:		Mar. 11, 1947	Red cell count	5.0 million
	Neutrophiles	70%		Hemoglobin	15 gm. %
	Lymphocytes	26%		Hematocrit	53%
	Eosinophiles	4%	Apr. 4, 1947	Red cell count	5.1 million
Feb. 28, 1947	Red cell count	8.4 million		Hemoglobin	15 gm. %
	Hemoglobin	22.8 gm. %			
	Platelets	130,000			
	Hematocrit	60%			
	Reticulocytes	2.6%			
	Bleeding time	1.5 min.			
	Clotting time	2.5 min.			

TABLE II  
Preoperative Biochemical Studies of the Blood

Date	Examination	Value	Date	Examination	Value	Remarks
Feb. 20, 1947	Serum protein	8 gm. %	Feb. 21, 1947	Cholesterol	130 mg. %	Electrolyte studies were not repeated because the values were within normal limits and were not expected to change.
	a. Globulin	2.8 gm. %		Sugar (blood)	97 mg. %	
	b. Albumin	5.2 gm. %		Non protein nitrogen	55 mg. %	
Mar. 2, 1947	*Prothrombin time	22 second		Serum sodium	374 mg. %	
Mar. 5, 1947	Blood urea nitrogen	24 mg. %		Serum potassium	17.1 mg. %	
	Icteric index	6		Serum calcium	9.7 mg. %	
	Uric acid	2.6 mg. %		Serum phosphorus	2.8 mg. %	
	Creatinin	2.2 mg. %		Plasma chlorides	486 mg. %	
				CO <sub>2</sub>	60 vol. %	

\* Control—17 seconds.

TABLE III  
Blood Oxygen Saturation

Preoperatively		Postoperatively	
* Determination	Value	† Value	Remarks
Hemoglobin	22.8 gm. %	15.4 gm. %	The critical level for cyanosis is 5 grams of reduced hemoglobin.
Blood oxygen capacity	30.2 vol. %	19.3 vol. %	
Arterial blood content (femoral)	19.1 vol. %	17.4 vol. %	
Venous blood content (brachial)	11.1 vol. %	11 vol. %	
Oxygen saturation arterial blood	63%	90%	
Oxygen saturation venous blood	40%	57%	
Arterial blood unsaturation	11.1 vol. %	—	
Reduced hemoglobin in arterial blood	8.4 gm. %	1.9 gm. %	
Venous blood unsaturation	19.1 vol. %	—	
Reduced hemoglobin in venous blood	14.4 gm. %	8.3 gm. %	
Average reduced hemoglobin (arterial + venous blood)	11.4 gm. %	5.1 gm. %	

\* Duplicate samples were examined and were found correct with 5% of error.

† Three days postoperatively.

TABLE IV  
Studies of Blood Volume and Pertinent Blood Constituents

Preoperatively			Postoperatively		
Date	Examination	Value	Date	Value	Remarks
Mar. 3, 1947	* Blood specific gravity	1.068	Mar. 10, 1947	1.056	* By the copper sulfate method ** Congo red method *** Normal: 37 c.c./kilo **** Normal: 51 c.c./kilo
	Plasma specific gravity	1.028		1.024	
	Plasma protein	7.82 gm. %		7.6 gm. %	
	Hemoglobin	21.5 gm. %		15 gm. %	
	Hematocrit	58%		42%	
Mar. 4, 1947	** Total blood volume	12,900 c.c.	Mar. 10, 1947	7,625 c.c.	
	Blood volume/kilo	161 c.c.		95 c.c.	
	*** Cell volume/kilo	99 c.c.		40 c.c.	
	**** Plasma volume/kilo	62 c.c.		55 c.c.	
	Per cent cell volume				
	Increase above normal	160%		Normal	
	Per cent plasma volume				
	Increase above normal	21%		Normal	

The radiologic findings were consistent with an arteriovenous fistula. Fluoroscopic and radiographic examination showed a normal configuration and size of the heart. All cardiac chambers were within normal limits. The long bones were normal.

Extensive laboratory studies were performed with special reference to physical characteristics of the circulating blood. Most of the pertinent studies were repeated after pneumonectomy. The essential laboratory data are reproduced in tables 1 through 4, and we shall refer to them whenever this is necessary. The vital capacity was 110 per cent; the venous pressure was 13 cm. of water; the circulation time from arm to tongue was 12 seconds and from arm to lung 9 seconds; the Wassermann reaction was negative.

The patient remained ambulatory while on the Medical Service, and suffered no syncopal episodes similar to those described previously.

On March 8, 1947 a total right pneumonectomy was performed by the Surgical Service. On the second postoperative day the patient was out of bed and was gradually made ambulatory. In spite of this, on the fifth day he developed phlebotrombosis of both lower extremities, necessitating ligation of the superficial femoral veins bilaterally. The subsequent clinical course was uneventful except for a low grade fever which subsided spontaneously.

## DISCUSSION

Hereditary hemorrhagic telangiectases were recognized by Rendu<sup>39</sup> in 1896, when he reported a case of hereditary epistaxis associated with multiple hemangiomas of the skin and mucous membranes. They were not described, however, as a clinical entity until 1901, when Osler<sup>33</sup> reported three cases of hereditary epistaxis associated with angiomas of the nasal septum and multiple telangiectases of other mucous membranes and of the skin. Since that time there have been well over 1,000 cases reported in the literature and the lesions have been found to involve practically any area of the body.<sup>5</sup>

The clinical manifestations of hemorrhagic hereditary telangiectases are quite varied depending upon the severity of the disease, the fragility of the

involved vessels and the site of involvement. Repeated hemorrhages result in secondary anemia, chronic debility and if severe, death.<sup>49</sup>

The hereditary nature of the disease has been fairly well established. A vascular defect is apparently transmitted as a dominant characteristic<sup>34</sup> affecting both sexes, but more frequently the female. In families with hereditary hemorrhagic telangiectases, approximately one-third of the mem-

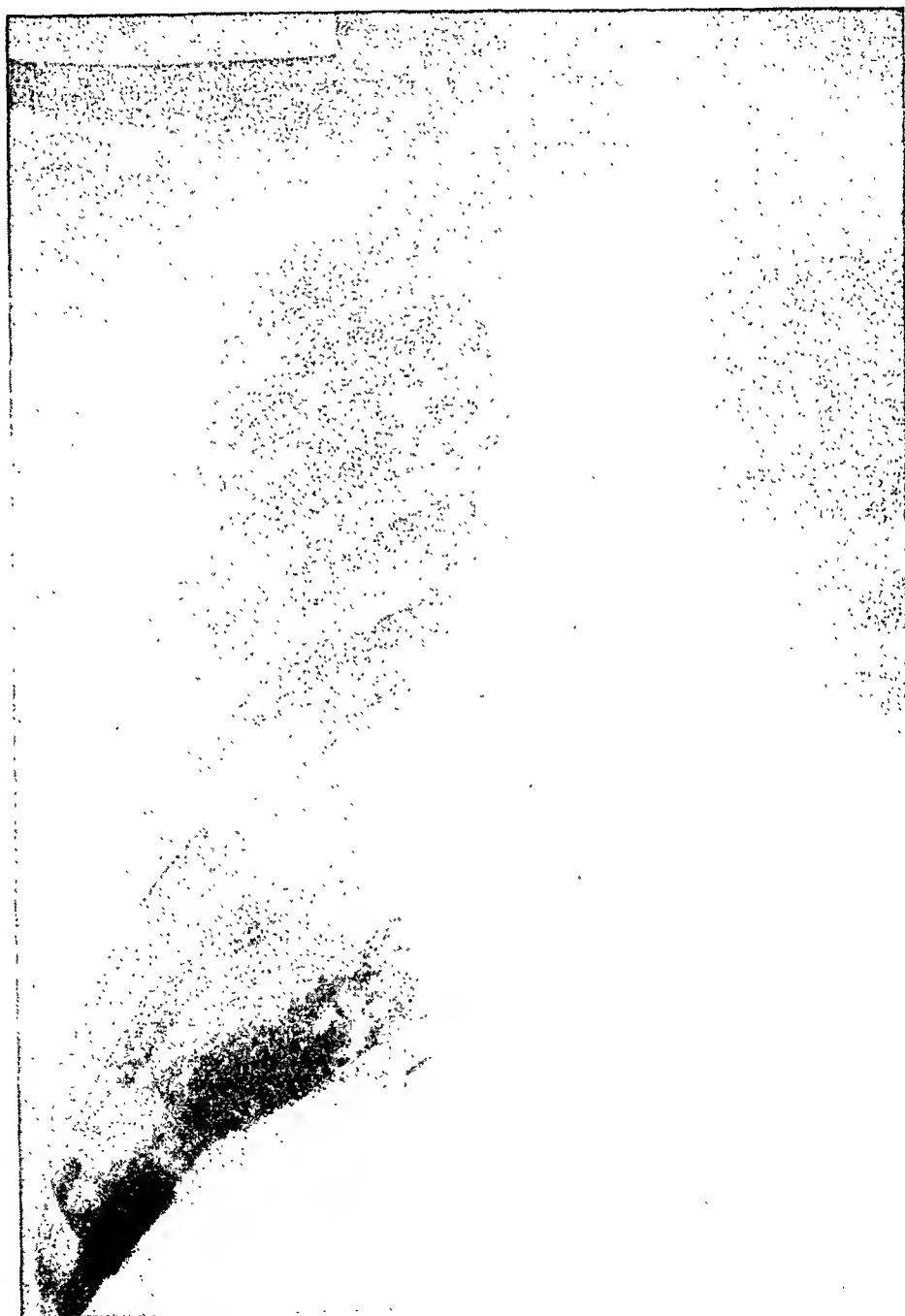


FIG. 8. *Case 2.* PA roentgenogram of the chest revealing the enlarged hilar vessels and the well-defined vascular "tumor."

bers are felt to be affected by this disorder.<sup>51</sup> The disease has been observed in three and four generations of families in whom they occur. Teahan<sup>51</sup> was able to trace it through six generations. According to some observers, the disease occurs spontaneously in 20 per cent of the cases.<sup>49</sup> Fitz-Hugh<sup>13</sup>



FIG. 9. *Case 2.* Right lateral roentgenogram of the chest: large abnormal pulmonary vessels extend from the hilum to the mass near the apex of the right lower lobe.

emphasized that the hereditary factor is constant, and that where it could not be demonstrated, this failure was due to atavism; one generation may be spared, only to have the disease insidiously appear in the next. The manifestations of the disease tend to decrease in severity in successive generations as well as to vary from one generation to another.

The most outstanding characteristic other than the hereditary tendency

is the formation of abnormal vessels, which bleed very easily even after slight trauma.

Singer and Wolfson<sup>45</sup> contended that the disease is usually a gross deviation of capillary formation, representing a generalized process rather than a local developmental defect of small vessels. There is frequently a marked photosensitivity as manifested in the family observed by us. Oc-

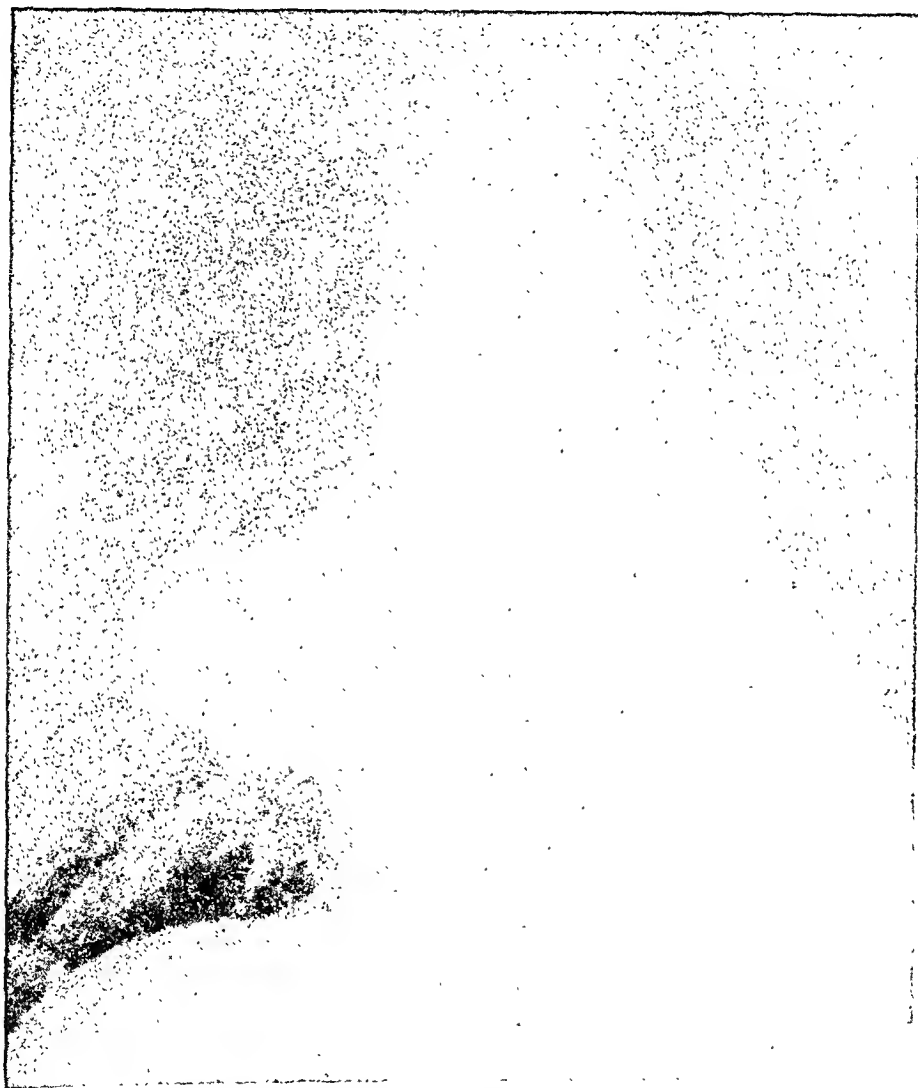


FIG. 10. *Case 2.* Angiogram: the dye is collected within the vascular mass; the vessels leading into the mass are also visualized and considerably dilated.

casionally telangiectases fail to exhibit hemorrhagic characteristics.<sup>28</sup> Perhaps Fingerland and Janousek<sup>12</sup> gave some explanation for these variations, when they found that the disease tends to be more severe in people with dark complexion. The abnormal vessels usually appear between the ages of 20 and 30, and attain full development in the fourth decade although the age of onset has varied between three months and 67 years of age. In the



family observed by us the skin lesion first appeared between the ages of 22 and 25.

The first case of pulmonary hemangioma was found incidentally by De Lange, De Vries and Rables<sup>11</sup> on postmortem examination of a two and one-half year old child. Later Wollstein<sup>57</sup> reported a malignant hemangioma of the lung in a four month old child which died from the disease and Hall<sup>17</sup> described similar postmortem findings in a 40 year old woman.

Although Rhodes had been credited with the first clinical description of hemangioma of the lung, Reading<sup>37</sup> earlier described the clinical triad of clubbing, cyanosis and polycythemia, associated with a pulmonary lesion which on postmortem examination proved to be a hemangioma of the lung. The patient died of a brain abscess. There were no additional clinical reports on this subject until Rhodes<sup>40</sup> in 1938 reported a case of cavernous hemangioma of the lung resulting in a fatal hemorrhage. The rarity of the disease is also attested by the fact that Sisson and his co-workers<sup>46</sup> found no record of it among 19,415 reviewed postmortem examinations at Johns Hopkins Hospital. The lesions may be either single or multiple. A review of the literature showed that of 15 cases reported, 10 patients had single pulmonary lesions determined radiologically or confirmed by operation or postmortem examination, whereas in five cases the lesions were multiple. In our cases, case 2 had multiple hemangiomata proved at operation, while A. E. had a single lesion demonstrated radiologically. Of the 15 cases reported in the literature<sup>1, 8, 15, 18, 20, 21, 25, 29, 42, 46, 47</sup> an association with hereditary hemorrhagic telangiectases was demonstrated in only three instances,<sup>1, 25, 42</sup> though nine patients had telangiectases of the nose, face or lips of a non-hereditary, non-hemorrhagic nature.<sup>1, 15, 20, 25, 29, 37, 42, 46</sup>

The clinical manifestations seem to be extremely variable. Small fistulae, like the one seen in the case of A. E., cause no complaints while large ones give rise to a complex of symptoms and signs which almost characteristically occurred in the 15 cases described previously and in our patient C. E. The symptoms depend upon the size and duration of the shunt. Arteriovenous fistulae of the lung may become fairly large before the typical triad of cyanosis, polycythemia and clubbing of the phalanges develops. According to some observations, approximately 30 per cent of the blood must be shunted before cyanosis becomes manifest in otherwise normal individuals.<sup>39</sup> A. E., who had a small arteriovenous fistula, has obviously not developed a sufficient shunt to produce objective findings. Because of that, an operation at this time was not deemed advisable. Further observation of the patient was, however, recommended, because he has already had spontaneous epistaxis and spontaneous hematuria and he may well develop spontaneous hemorrhage from the lung.

The symptoms of this disease usually become manifest in the third decade of life. Our patients were 26 and 29 years of age respectively. Except for the clubbing of the fingers and toes the exact origin of which remains obscure, the chief symptoms of the disease are apparently due to chronic anoxemia,

produced by incomplete aeration of the blood in the lungs. This stimulates the erythropoietic system resulting in polycythemia. Other symptoms such as dyspnea on exertion, weakness, palpitation, dizziness, numbness, faintness, diplopia, thick speech, hemoptysis, emesis and chest pain represent secondary phenomena.

Our patient (case 2) showed the typical triad of cyanosis, polycythemia and clubbing of the fingers and toes, and also other symptoms related to anoxemia.

Cyanosis has varied as to the time of appearance from shortly after birth to a period only several years prior to the time when the patients sought medical attention.<sup>29</sup> In our patient (case 2) the cyanosis became manifest at the age of 22. Clubbing of the fingers usually develops shortly after cyanosis becomes manifest.

The effects of anoxemia due to pulmonary shunt and the compensatory mechanisms are interesting from a clinical and a laboratory point of view. The compensatory changes consist of an increase of blood volume (affecting the cell volume rather than the plasma volume), increased hemoglobin concentration and an increase of erythrocytes closely paralleling the changes seen in the relative anoxia of subjects living at high altitudes for long periods of time. In both conditions these changes are proportional to the degree of unsaturation of arterial blood regardless of geographical location or race.<sup>19</sup> Barcroft<sup>4</sup> in 1923 pointed out that residents living at high altitudes had decreased blood oxygen tension with an increased cell volume and red blood cell concentration. McFarland et al.<sup>31</sup> who examined 200 civilian pilots found the red cell count above six million in 50 per cent of flying personnel. Smith et al.<sup>47</sup> found 19 per cent increase of cell volume in residents at high altitudes, but normal plasma volume. Certain observations tend to substantiate the contention that polycythemia of the newborn is also due to low intrauterine oxygen tension.<sup>14</sup> Hurtado et al.<sup>19</sup> found that the response to acute anoxia was short, the increase of the red cells was transitory, due largely to hemo-concentration, but as the subjects remained exposed to low oxygen tension, the increased erythropoietic activity became a constant factor, causing an increase of reticulocytes (2 to 4 per cent) and of the cell volume without a concomitant increase of plasma volume and without change of plasma proteins. This change lasted as long as the subjects remained in this environment and was proportional to the degree and duration of the anoxia. It is remarkable how well patients with pulmonary arteriovenous fistula conform to the same principles.<sup>1, 15, 18</sup> In several instances red cell counts up to 11.4 million and a corresponding rise of the hemoglobin content were observed.<sup>15, 40, 46</sup> In both conditions there is an inverse ratio between the polycythemia and the arterial oxygen saturation.<sup>1, 15, 18, 19</sup> In view of these findings, it is not surprising that the polycythemia reflects fairly accurately the degree of arteriovenous shunt in cases of pulmonary arteriovenous fistulae. Values of 70 per cent of oxygen saturation were recorded in three cases.<sup>15, 40, 46</sup> Case 2 had only 63 per cent oxygen saturation (see

table 3). His cell volume rose 160 per cent above the normal value, while the plasma volume increased only by 21 per cent (see table 4). It is probable that our and the other patients obtained maximal compensation (see table 3).<sup>1, 15, 18</sup> If the fistula continued to increase in size, one should expect eventually a decrease of the red cell count due to depression of the bone marrow secondary to anoxia.<sup>19</sup> The critical point of arterial oxygen saturation at which suppression of erythropoiesis might be expected is not known. Taussig and Blalock observed that children suffering from congenital heart disease developed polycythemia when the arterial oxygen saturation was only 36.3 per cent. Indeed it appeared that in their cases an arterial blood saturation of 66 per cent or lower was necessary, before a compensatory polycythemia became manifest. One of those cases, however, with only 20.6 per cent of saturation, did show evidence of bone marrow suppression and anemia. Normal blood counts or slight anemias also occurred in patients with pulmonary arteriovenous fistulae, when they were associated with another disease or frequent excessive hemorrhages.<sup>25, 42</sup>

Already in 1878 Bert<sup>6</sup> expressed the opinion that the erythroblastic activity of the bone marrow was governed by arterial oxygen tension. Probably due to physiological adjustment there is a less significant erythropoietic response in chronic anoxemia than in the subacute phase.<sup>19</sup> Immature red cells and marked increase of reticulocytes are therefore not usually seen in pulmonary arteriovenous fistulae. Our patient showed no nucleated red cells and a reticulocyte count of 2.6 per cent. In contradistinction to polycythemia vera there was no increased activity of the granulocytic series, and the spleen was not enlarged.

Chronic anoxemia of whatever origin does not modify permanently the activity of the erythropoietic system.<sup>19</sup> This was conclusively demonstrated in "altitude polycythemia" and was also confirmed in the patient (case 2), who three days after pneumonectomy showed a return to normal of the red cell count, total cell volume, and hemoglobin concentration (see tables 1, 2, and 4).

The lack of cardiac enlargement was significant and essentially in conformity with the findings of other writers on this subject. An enlarged heart was observed in only two cases, one of whom had mitral stenosis.<sup>25</sup> In the other case the enlargement was due to congestive failure secondary to chronic myocardial disease.<sup>46</sup> Kennedy and Burwell<sup>22</sup> have noted that in chronic peripheral arteriovenous fistulae there is an increase in cardiac output, blood volume, and venous oxygen tension near the fistula, and mild to moderate cardiac hypertrophy. The lack of cardiac hypertrophy in cases of chronic pulmonary arteriovenous fistulae has been attributed to the low pressure in the pulmonary circulation.<sup>15</sup>

The blood pressure is usually within normal limits.<sup>42</sup> A murmur is commonly heard over the tumor mass and is transmitted to the heart; it is continuous, with maximal intensity in late systole and early diastole. The murmur is loudest on deep inspiration and hardly audible on expiration.<sup>21</sup>

<sup>25, 42</sup> This, however, is not sufficiently pathognomonic, since murmurs have been described during other phases of the cardiac cycle and over the heart only. No murmur of any kind was recorded in five cases.<sup>1, 18, 25, 42, 47</sup> One of our patients (case 2) had a purely diastolic murmur, of increased intensity on deep inspiration. The murmur disappeared after pneumonectomy. The other patient (case 1) had no cardiac murmurs.

Pulsation of the carotids and in the suprasternal notch may be very prominent. In the majority of cases the electrocardiograms were normal. One case<sup>21</sup> showed marked right axis deviation. This possibility should be kept in mind in differentiation of this condition from congenital heart disease. In case 1 the electrocardiogram was normal. The other patient (case 2) had marked left axis deviation. Electrocardiograms taken during the operation showed, for the most part, nodal tachycardia with auricular and ventricular extrasystoles. During bronchoscopy the tracing showed a supraventricular tachycardia with a rate of 150 per minute. A tracing taken the day following operation showed a smaller S<sub>2</sub> and S<sub>3</sub>. CF leads showed a "V" QRS in CF<sub>1, 2, 3, 4</sub> and 5.\* The electrocardiographic findings were difficult to interpret because the heart was not in transverse position nor was there any apparent left sided hypertrophy.

The prognosis in cases of pulmonary arteriovenous fistulae has been good especially in those operated upon. Two patients<sup>8, 42</sup> died following a rupture of the fistula into a bronchus with a hemorrhage; one patient<sup>46</sup> died shortly after cardio-angiography and six<sup>1, 18, 20, 21, 25</sup> who have been operated upon are living and well. Other patients remain under medical observation because the disease is relatively asymptomatic, or because an operation was refused. The possibility of a hemorrhage as well as vascular thrombosis due to increased viscosity of the blood, must always be kept in mind in these patients.

### PATHOLOGY

Hereditary telangiectases are characterized by disseminated abnormalities of capillaries, small venules and small arterioles, which have the appearance of hemangiomata or telangiectases or both.<sup>53</sup> They vary from typical spider nevi to pea size hemangiomata.<sup>34, 49</sup> They occur most commonly on the skin and mucous membranes, but may involve any organ. The cutaneous or mucosal vascular lesions are composed of dilated small vessels which histologically comprise a single layer of endothelium underneath a much thinned layer of epithelium. The absence of muscular and elastic layers of the vessel wall is conspicuous. The vessels are fragile and rupture easily. Thrombosis is quite frequent<sup>49</sup> and possibly accounts for occasional disappearance of the lesions in certain areas. Neumark<sup>32</sup> has shown that in addition to the hyperplasia of the small vascular radicles there are changes in the connective tissue consisting of degeneration of conjunc-

\* We wish to express our appreciation to Lt. Walter Zimdahl for the electrocardiographic studies.



FIG. 11. *Case 2.* Specimen of the removed lung: the posterior wall of the "cavernous hemangioma" has been resected. The dilated vein and traversing trabeculae are demonstrated. The probe is within the pulmonary artery, which enters the aneurysmal cavity.

tive and elastic fibers. Numerous newly formed vascular buds suggest angioblastic activity. Arteriovenous fistulae of the lung, causing intrapulmonary tumefactions and giving rise to a now well-defined clinical complex are of particular interest in this presentation, and merit a more detailed discussion. The literature contains very few references to this subject, and



FIG. 12. Case 2. The pulmonary artery is opened; both sides of the fistula are demonstrated.

the pulmonary lesions which occurred either isolated or in association with the classical manifestations of hereditary telangiectases have been variously described as cavernous hemangioma, arteriovenous aneurysm or arteriovenous fistulae. The difference in terminology reflects the evolution of the concepts regarding the pathogenesis of "vascular tumors" or abnormalities as a whole.



FIG. 13. *Case 2.* One year after operation, the telangiectases of the face and lips have disappeared.

Reid<sup>38</sup> advanced the view that cirroid aneurysms, pulsating angiomas, and possibly simple angiomas represent essentially arteriovenous aneurysms, with abnormal arteriovenous communications. This eliminates the capillary bed, which is the normal communication between arterial and venous systems and leads to clinical symptoms depending on the size and location of the vascular abnormality. The arteriovenous communication may be either acquired or of congenital origin. The pulmonary arteriovenous fistulae so far reported and those observed by us belong obviously to the latter group. The occurrence of such congenital fistulae is readily explained by the development of arteries and veins from a common capillary plexus. Their ultimate fate is determined by the size of these communications and the pressures to which they are subjected.

The pathological alterations encountered in pulmonary arteriovenous fistulae are less familiar, and may be best described by referring to individual descriptions found in the literature. In seven of 15 reviewed cases of pulmonary arteriovenous fistulae the specimens obtained at surgery or postmortem examinations were subjected to pathological studies. The changes consisted uniformly of a distended afferent artery and distended efferent veins. Between the arterial and venous systems there is either a direct communication through one or several larger vascular trunks, or a tangle of more or less distended vessels instead of capillaries. Owing to the fact that the arterial pressure is transmitted directly into the malformed vessels and into the veins, these become increasingly dilated. Degenerative changes arise in the walls and in some cases ruptures occur. Because of these, new pathological communications may arise between the vessels, which increase the circulatory disturbance still further. Ruptures of vessels may also give rise to hemorrhages in surrounding areas. In the case of Jones and Thompson<sup>21</sup> there were also other anomalies; the middle lobe was absent. The right upper lobe had many blue, thin-walled "varicosities" over its anterior surface, and there appeared to be a very thin-walled sac filled with dark blood projecting from the lower aspect of the upper lobe at the site corresponding to where the middle lobe should have been. There were communications between the multilocular hemangiomatous cavities, the superficial varicosities, and the inferior pulmonary vein. The superior pulmonary vein was absent. Microscopically, the cavities are usually lined by mesothelial cells lying on a fibrous connective tissue wall.

Pathological studies of the specimen obtained from our patient (case 2) showed a large thin-walled vascular sac in the posterior portion of the right lower lobe near the apex, containing approximately 22 c.c. of blood. Three other similar sacs, measuring less than 1 cm. in diameter, were scattered within the lower lobe, projecting partly on the pleural surface of the lung. The right upper lobe contained two similar lesions and one was observed in the middle lobe. On dissection, the large arteriovenous fistula in the lower lobe was composed of two arteries, a dilated sac and the inferior pulmonary vein. The sac interposed between the communicating vessels was divided into multiple locules by fibrous strands traversing the cavity. Communicating vessels could also be demonstrated in all other fistulae. The small cavities resemble a large sinusoidal or cavernous network. The histological changes conformed essentially with those described in other cases.\*

On the basis of our observations it seems justified to assume that congenital arteriovenous pulmonary fistulae result from a gross deviation of capillary formation, and appear as single or multiple lesions, quite frequently associated with hereditary telangiectases. We should, therefore, prefer to reject the term of "varicosities" as applied to this disease.

\* We wish to express our appreciation to Lt. Col. Robert W. Holmes for the pathological studies of the specimen.



## RADIOLOGICAL ASPECT

Pulmonary arteriovenous fistulae, or cavernous hemangiomata, thus far reported in the literature, present sufficiently characteristic features to permit a definition of radiologic diagnostic criteria. They have been adequately described by Lindgren,<sup>25</sup> and our own cases confirm his observations.

In all cases circumscribed, slightly lobulated shadows of increased density were observed in the lung. Occasionally the lesions were multiple and bilateral. The intrapulmonary opacities were connected with the hilar vessels by broad, tortuous bands of increased density, representing a distended branch of the pulmonary artery and a dilated pulmonary vein, both of which opened into a tumor-like vascular sac. Usually two such vessels were observed, but in some instances more anomalous vessels were encountered. The communicating vessels lie in different planes, and it is usually necessary to obtain films in several projections to demonstrate the anatomical relations of the abnormal vessels and the tumor, produced by this abnormality. Fluoroscopic examination may reveal pulsations of the tumor. The tumor may show variations in size, depending on change of the intrathoracic pressure. On Valsalva test (deep inspiration, followed by forced expiration against the closed glottis) the mass may become smaller. Mueller's test (deep expiration, followed by forced inspiration against the closed glottis) causes an increase of the mass. The variations in size may be difficult to observe since the change is not very marked. The significance of pulsations of tumors must be carefully evaluated. It is rather difficult to differentiate definitely between spontaneous and transmitted pulsations, particularly when a tumor is located near the hilum, and only a part of the circumference of the tumor can be demonstrated. The pulsation of peripherally located lesions can be proved more readily by appropriate kymographic studies.

Lindgren<sup>25</sup> stressed the importance of careful studies of the pulmonary vessels and their relation to a pulmonary tumor. This, in his opinion, is the most reliable criterion, permitting a correct radiologic diagnosis. Even small arteriovenous fistulae show at least two vessels, connecting them with the hilar vessels. These vessels are larger than other vessels in the same region and follow a different course. The more peripherally located tumor can not be separated from the apparently abnormal vessels.

The radiologic diagnosis may be quite difficult. Small cysts, adenomata, metastatic lesions and tuberculomata are only some of the lesions which may offer differential problems. Aneurysms of the branches of the pulmonary artery may also cause round opacities, simulating other lesions. Lindgren<sup>25</sup> points out that they should be distinguished from other changes by the demonstrable vascular origin of the opacity and from the arteriovenous fistula by the fact that in the latter, the vessels are more distended, and at least two can usually be demonstrated. It is also well to remember that an aneurysm of the pulmonary artery without a shunt does not cause cyanosis, which is an important symptom in cases of arteriovenous fistulae.

Intrapulmonary hemorrhages resulting from a rupture of the dilated vessel cause occasionally irregular densities, and even segmental atelectases, obscuring the primary lesion, and thereby add to the diagnostic difficulties. There, too, careful observation of anomalous vascular bands adjacent to the irregular densities aids materially in arriving at a correct diagnosis.

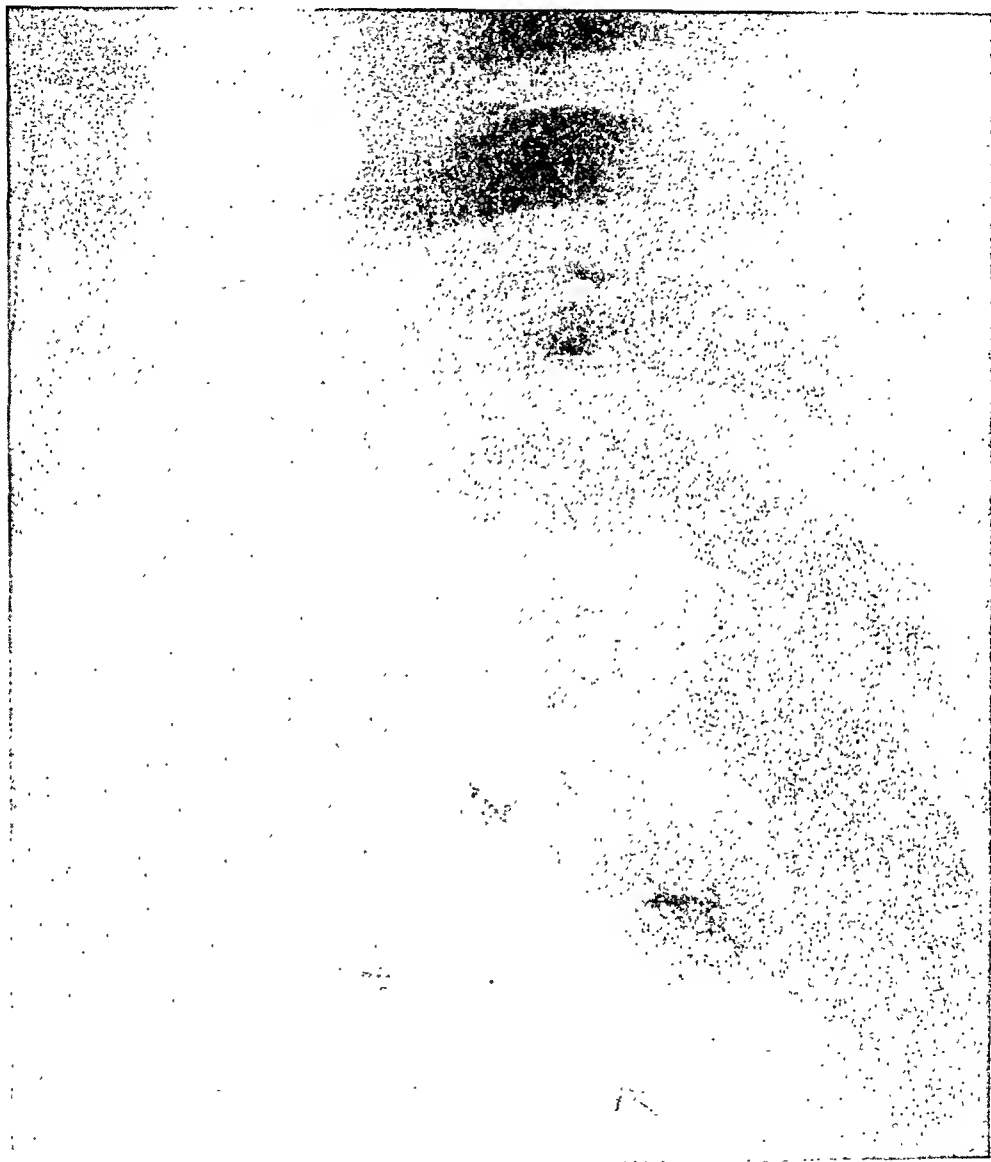


FIG. 14. *Case 3.* PA roentgenogram of the chest showing two round opacities at the left base, representing pulmonary "hemangiomas."

The lack of cardiac enlargement mentioned previously is rather conspicuous in cases of pulmonary arteriovenous fistulae. This is in striking contrast to the arteriovenous fistulae in the greater circulation, and most likely contributes to the diagnostic difficulties from the radiologic point of view when the clinical history is not available.



FIG. 15. *Case 3.* Lateral view of the chest showing the "hemangiomata" within the dorsal segment of the left lower lobe.

The routine radiologic examination can be advantageously supplemented by body-section radiography and angiography. The planigrams of the case reported by Jones and Thompson<sup>21</sup> demonstrated very clearly a multilobulated mass arising from the branches of the right pulmonary artery. The connecting branches were markedly dilated and their course was abnormal.

Angiography, when successful, demonstrates clearly the vascular character of the tumor, and its connection with the pulmonary vessels. Intravenous injection of 70 per cent Diodrast seems to be preferable to introduc-

tion of the dye after catheterization, because of suggested greater inherent danger in the latter method. It should be emphasized that special caution must be exercised in the use of angiography in cases of arteriovenous fistulae. Among other dangers, the possibility of thrombosis must be kept in mind. The high cell volume, associated with this disease, makes the possibility of thrombosis very real. Congenital pulmonary arteriovenous fistulae are not always single lesions. On the contrary, the evidence now at hand indicates that they are perhaps more frequently multiple, and may occur in both lungs. The lesions demonstrated radiologically represent usually the largest fistulae in a given case, but by no means the only one. In addition, there may be several or even numerous small "cavernous hemangiomas," located underneath the visceral pleura, producing small irregular prominences on the pleural surface of the lung, but not extending appreciably into the pulmonary parenchyma.

It is not at all surprising that small sub-pleural "hemangiomas," in close contact with the structures of the thoracic cage, escape radiologic detection on routine examination. The lack of the essential contrast of densities accounts for this. It may be necessary, at times, to include a diagnostic pneumothorax as an additional procedure to those already discussed. It is essential to obtain several films, in various projections, in order to demonstrate the pleural surface of the lung, along most of its circumference. A better visualization of the "hemangiomas" can be obtained on deep inspiration followed by forced expiration against the closed glottis (Valsalva test), and the exposures should be preferably made under those conditions.

The pulmonary lesions may occasionally be associated with hypertrophic osteoarthropathy, as seen in congenital heart diseases or chronic pulmonary diseases. The skeleton in our cases was normal.

### TREATMENT

Certain observations appear pertinent in relation to the treatment of pulmonary arteriovenous fistulae. As we mentioned previously the clinical manifestations of the disease depend on the size of the shunt within the pulmonary circulation. Small fistulae, usually asymptomatic, may require no treatment at all. It is advisable, however, to observe those patients over prolonged periods of time, since existing fistulae may increase in size, and others may become manifest either in the already involved or in the contralateral lung. Serial roentgenograms will in such cases reveal the evolution of these lesions. Repeated blood counts may prove an adequate indicator of the progress of the disease, reflected in the secondary polycythemia.

Symptomatic arteriovenous fistulae necessitate surgical intervention. Total pneumonectomy, lobectomy or partial resection of a lobe have been performed, depending on the findings ascertained on thoracotomy of individual cases. Of eight patients subjected to surgery, three had a total pneumonectomy. In Jones'<sup>21</sup> case there was no superior pulmonary vein; in

Adams'<sup>1</sup> case multiple lesions involved more than one lobe; and in Shennstone's case there were such large vessels around the hilum that pneumonectomy was deemed necessary. Pennoyer<sup>35</sup> emphasized a similarly increased vascularity in the region of peripheral arteriovenous fistulae as a characteristic feature of the disease. Lobectomy was performed in two cases. In two cases, the operation was limited to local resection of the lesions.<sup>20, 25</sup> Janes<sup>20</sup> resected locally two lesions, one of which was present in each lower lobe. In one case the operation was limited to lingulectomy.<sup>25</sup>

Venous thrombosis deserves consideration in the management of these cases because of the marked polycythemia and increased blood viscosity. Although anticoagulants were not used in this case because of danger of postoperative hemorrhage, serious thought should be given to this approach in view of the postoperative complication of phlebothrombosis, which may have been prevented with dicumarol.

Phlebotomy with the withdrawal of blood replaced by plasma may also be of some value.

#### SUMMARY

1. A family with hemorrhagic hereditary telangiectases has been reported and the clinical manifestations and pathogenesis of the disease reviewed.

2. Two members of this family had visceral involvement consisting of pulmonary arteriovenous fistulae.

3. The clinical and physio-pathological aspects of this complication have been discussed.

4. The pathological changes in pulmonary arteriovenous fistulae have been presented.

5. The radiologic diagnostic criteria of the disease have been described.

6. Treatment has been considered.

#### ADDENDUM

Since the completion of this paper another case of hereditary hemorrhagic telangiectases complicated by an arteriovenous fistula of the lung has come under our care. The patient previously had a lobectomy elsewhere and is included here as a follow-up only.

C. S., a 28 year old white male, whose father had bleeding telangiectases of the face and frequent epistaxis, was in good health until June, 1943 when he developed telangiectases over the malar prominences and the bridge of the nose. These were accompanied by frequent epistaxis. About six months later he began to complain of night sweats, weakness and malaise without fever. The patient developed marked cyanosis associated with polycythemia and increased blood volume. Roentgenologic examination of the chest revealed two round opacities in the left lower lobe and anomalous vessels connecting these lesions with the hilar vessels. The findings were consistent with arteriovenous fistula. The left lower lobe was resected with complete relief of cyanosis, polycythemia and previous symptoms of weakness and malaise. He has remained free of symptoms to date except for bleeding telangiectases of the face and mucous membranes of the mouth and the upper respiratory tract. Laryngoscopic examination, at present admission, showed numerous telangiectases within the pharynx, larynx and trachea.

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# PSEUDOHEMOPHILIA \*

By HARRY L. HALLIWELL, M.D., and LAWRENCE BRIGHAM, M.D.

THIS report deals with a family of "bleeders" whose hemorrhagic diathesis fulfills the diagnostic criteria of "pseudohemophilia" as recently presented by Estren, Médal and Dameshek.<sup>1</sup> These authors have reviewed the literature and classified 62 patients who exhibited a tendency toward abnormal bleeding as cases of pseudohemophilia. Either sex is involved, and the striking laboratory finding is a prolonged bleeding time in the presence of normal blood platelets and normal coagulation time.

The cases presented in this report are males, five in number, ranging in age from six to 77 years. Chart 1 shows the family relationship of the five "bleeders."

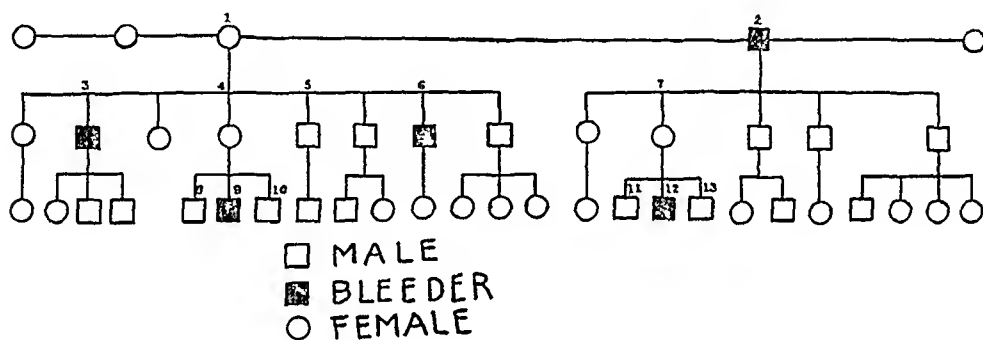


CHART 1. Only those individuals with an assigned number are discussed in the text.

## CASE REPORTS

*Case 2* is a 77 year old male who had severe bleeding from minor cuts as a youth. While a youth in Europe, bleeding from minor cuts was stopped by "burning the wounds" and "tight bandages." The bleeding tendency gradually diminished in severity as he grew older. At about 50 years of age he lost all symptoms of the disease.

*Case 3* is a 27 year old male. Physical examination revealed no enlargement of the spleen. Since early childhood he has experienced severe bleeding from minor lacerations. Profuse bleeding followed extraction of teeth five years ago. Patient has never been hospitalized and at present his symptoms are mild.

*Case 6*, brother of *Case 3*, is a severe bleeder and has had many hospital admissions.

*First hospital admission* was on June 25, 1910 at age of two years because of purulent conjunctivitis and staphyloma of the right cornea. Physical examination revealed no other abnormal findings. The right eye was enucleated. Severe hemorrhage followed the operation, but no bleeding point could be found. The operative wound was packed and bleeding stopped after 19 days.

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*Second hospital admission* was on March 17, 1914 for pain and swelling of the left thigh and hip of three weeks' duration. Physical examination revealed that the left hip was held in flexion and there was pain and limitation of movement. Roentgenogram of the region revealed no bony abnormality. The clinical impression was bleeding into the hip joint. No laboratory data were recorded.

*Third hospital admission* was for re-check of hip condition. Good function was discovered.

*Fourth hospital admission* was on January 26, 1940 because of a "bleeding out" on patient's lip. Injury had occurred 10 days prior to admission. Physical examination revealed blood oozing from a mucosal tear of lower lip. A direct transfusion of 250 c.c. of whole blood was given the patient on January 27, 1940 with cessation of bleeding. Laboratory data: urine examination negative; red blood cell count  $4\frac{1}{2}$  million. Hemoglobin reported as 90 per cent.

*Fifth hospital admission* was on May 5, 1941 for a bleeding laceration of the eyelid occurring three days prior to admission. Laceration continued to ooze for three days after hospital entry before stopping. Laboratory data: Platelets normal in number. Red blood cell count 4 million; hemoglobin 14 grams; white blood cell count 10 thousand with normal differential count.

*Sixth hospital admission* was on May 9, 1942 because of alveolar abscess. Owing to past history of bleeding, bleeding and clotting tests were done. Coagulation time, 9 minutes by "test tube method." Bleeding time was reported as 1 minute. Method used was not recorded.

*Seventh hospital admission* was on June 8, 1942 for an alveolar abscess. Clotting time was normal. No bleeding time was reported. On June 9, 1942 tooth was extracted. Despite many tannic acid and adrenalin packs, silver nitrate cautery, snake venom therapy, parenteral hykinone and local thromboplastin, the tooth socket continued to bleed for 10 days. Fifteen hundred c.c. of whole blood (citrated) were used for replacement.

*Admission in 1947* to a second hospital following eight weeks of oozing from dental sockets after extractions. He received a direct transfusion with cessation of bleeding.

*Case 12* was a male, age 17 years.

*First admission* was on September 29, 1934 at four years of age for bleeding following tooth extraction. Physical examination not remarkable. Laboratory data: Urine negative; red blood count 2 million; hemoglobin 35 per cent. Platelets: many on smear. Coagulation time by three tube method was  $7\frac{1}{2}$  minutes. Bleeding time was three minutes. Method used was not recorded. White blood cell count was 9 thousand. Transfusion of 300 c.c. of citrated blood was given. Packings and thromboplastin were used locally. Bleeding gradually stopped after six days.

*Second admission* was on August 6, 1935 for alveolar abscess.

*Third admission* was on September 25, 1936 for bleeding about lower incisors. Teeth were removed and pressure packs used to control hemorrhage. Cessation of bleeding occurred after six to eight hours.

*Fourth admission* was on August 23, 1940 for hematoma and bleeding laceration of forehead of 24 hours' duration. Evacuation of organized clot in original wound with deep suturing of wound resulted in hemostasis. Discharged four days after admission.

*Fifth admission* was April 15, 1941 with chief complaint of swelling of left knee following traumatic injury. Physical examination revealed swollen left knee with ecchymosis on antero-medial aspect. Impression was traumatic hydrarthrosis. Roentgenogram revealed calcifications in soft tissue about knee. Knee joint was not tapped, but examination revealed fluid. On April 14 patient had a spontaneous epistaxis which ceased after two days with nasal packings. Laboratory data: Prothrombin

time 56 per cent; hemoglobin 10 grams; coagulation time by three tube method 10 minutes; bleeding time 1 minute (method used not recorded); red blood cells 4 million, white blood cells 12,000.

*Sixth hospital admission* was on August 22, 1941 for tenosynovitis. No laboratory data.

*Seventh admission* was on January 24, 1942 for bleeding hematoma of lower lip following a fall. Bleeding stopped two days after admission. He received 50 c.c. of whole blood intramuscularly. Urine examination was negative. Hemoglobin 14 grams.

*Eighth admission* was for swelling of the right thigh. Eight days prior to admission, patient's thigh began to swell following a slight injury. There was no known trauma to knee directly. Physical examination revealed a 10 by 5 inch ecchymotic area over the lower medial surface of the thigh which was soft and painful. The right patella floated and the knee was swollen. Discharge diagnosis was hemarthrosis of right knee. Laboratory data: Red blood count 4.16; white blood count 15.8; hemoglobin 11.5 grams. Roentgenogram of the knee revealed no bony abnormality.

*Ninth hospital admission* was for removal of teeth on September 24, 1946. Physical examination revealed dental caries and an ecchymotic area over the right shin. Bleeding time done at this time by Duke method was 5 minutes. Following removal of two teeth, patient bled profusely for four days. An immediate postoperative transfusion of 500 c.c. of whole citrated blood was given. On September 29 a transfusion of 500 c.c. of citrated blood was given because of continued blood loss. On September 30 patient received 25 c.c. of whole blood directly and bleeding stopped for 18 hours. Bleeding began again despite topical thrombin, oxycel and gauze packs. On October 1 a direct transfusion of 140 c.c. of blood resulted in cessation of bleeding abruptly for 24 hours. Tooth sockets began to ooze slightly at that time but packing with tannic acid checked further ooze. On October 3 prothrombin activity was 75 per cent of normal. On October 8 patient received 500 c.c. of whole citrated blood for replacement purpose. Laboratory data on October 7: Red blood count 3.5; hemoglobin 12.3; coagulation time by three tube method 9 minutes; bleeding time by Duke method 4.5 minutes.

*Case 9* is a male, age six years.

*First hospital admission* was on July 1946 for an oozing laceration on the right buttock sustained eight days prior to admission. Physical examination revealed dental caries, hypertrophied tonsils and two ecchymotic areas over lower back. A two-inch oozing laceration was evident on the right buttock. Patient gave a history of abnormally easy bruising. Laboratory data on admission before any transfusion revealed clotting time of 10 minutes with normal clot retraction. Prothrombin time was 70 per cent of normal. Red blood count was 3 million; hemoglobin 9.7; white blood count 11.9. No bleeding time was recorded. Bleeding continued despite many local measures and red blood cell count fell to 2.1 and hemoglobin to 7 grams on July 19. On July 20, 700 c.c. of whole citrated blood were given. On July 22 patient was brought to operating room and wound was packed with oxycel and deep sutures inserted. Postoperatively bleeding ceased. On July 31, 1946 clotting time by three tube method was 11 minutes and bleeding time 5 minutes.

*Second hospital admission* was on April 23, 1947 for a bleeding laceration of left forehead. Pressure dressing appeared to stop bleeding and patient was discharged two days after admission.

*Third hospital admission* was on April 27, 1947 for bleeding laceration for which patient had been admitted four days previously. Laboratory data on admission: Red blood count 4.1; hemoglobin 11.6; clot retraction normal; clotting time 2½ minutes by one tube method; bleeding time by Duke method greater than 15 minutes. On April 30 patient received 250 c.c. of blood, and a tight pressure dressing resulted in ces-

sation of bleeding for 24 hours. Because of persistent oozing, patient was brought to operating room on May 1 for suturing of wound. He received 250 c.c. of fresh citrated blood on this date. On May 3, 1946 red blood cell count was 3.9; hemoglobin 12; platelets plentiful on blood smear. Laceration was still bleeding. Wound was packed with gauze in an attempt to stop bleeding. On May 4 bleeding stopped. On May 12 bleeding time was greater than 15 minutes; clotting time 7 minutes; tourniquet test negative; platelet count 220,000. On May 21 patient was brought to operating room where gauze packing was removed. Patient received 130 c.c. of whole blood by direct transfusion before the surgical procedure. Granulation tissue was cut away without any abnormal bleeding. Nineteen hours postoperatively bleeding time was 6 minutes. Sixty-seven hours after operation, at time of discharge, bleeding time had lengthened to 8.5 minutes.

### AUTOPSY REPORTS

The cause of the deaths of Cases 8 and 11 cannot definitely be decided. Brief summaries of the autopsy findings follow. It will be noted that both cases showed pathological hemorrhages at postmortem examination.

*Case 8*, a male, was stillborn on April 18, 1935. Weight was 10.5 pounds. Delivery was by a breech extraction. The right adrenal was completely destroyed by hemorrhage.

*Case 11*, a male, was born on May 28, 1939 by breech delivery. Shortly after birth, rapid ecchymosis appeared in the right hand and both feet. On May 29 patient died after experiencing some respiratory difficulty. Multiple hemorrhagic extravasations were found within the skull, spleen and in various locations in the soft tissues of neck and trunk. Multiple petechiae in the heart (subpericardially) and in the skin of the upper and lower extremities were noted. A persistence of fetal type of blood circulation was present.

### LABORATORY FINDINGS

Hematological studies of Cases 2, 3, 6, 9, and 12, all clinical bleeders, revealed normal values for red blood cell count, hemoglobin and white blood cell count. Blood smears showed normal white blood cells and normal differential counts as well as no diminution in platelets. During his first hospital admission, Case 12 had a red blood cell count of 1.9 million and a hemoglobin of 5 grams which was the result of blood loss. The severity of this blood loss resulting from small oozing lacerations or tooth extractions is emphasized by the fact that Case 6 received 1500 c.c. of blood during his sixth hospital admission; Case 9, 1200 c.c. during his first hospital stay; and Case 12, 1700 c.c. during his ninth hospital admission. At the time of this study no individuals showed anemia secondary to chronic blood loss.

TABLE I  
May 1947

Case	Coagulation Times
2	7 minutes
3	8
6	5½
9	7
12	4½

*Coagulation Time.* The determination of coagulation time was according to the Lee-White three tube method. Normal values accepted were between two and 10 minutes.<sup>2</sup>

Table 1 records the values obtained—all within normal limits.

*Bleeding Time.* The Duke method was used, in which a small cut was made on the volar surface of a digit. The cut was deep enough to cause oozing without pressure. At intervals of 30 seconds the drops of blood were removed by means of a blotter without touching the skin. According to Wintrobe,<sup>2</sup> a bleeding time greater than five minutes should be considered abnormal. Normal controls<sup>14</sup> for this method ranged from 2 to 4.5 minutes. Only those bleeding times considered valid during past hospital admissions are included in the table below. All but Case 2 showed a definitely abnormal bleeding time.

TABLE II  
Bleeding Times

During Past Hospital Admissions				During Present Study				
	7-31-46	9-24-46	10-7-46	4-30-47	5-12-47	5-22-47	5-25-47	6-9-47
Case 2					4			2½
3					7½			
6					>15			
9	5			>15	>15	6	8½	
12		5	4½	7½	5½			

The platelet counts on all five cases were normal. Blood smears also indicated platelets to be plentiful.

TABLE III

Case	Platelet Count
2	200,000
3	250,000
6	200,000
9	220,000
12	280,000

All platelet counts were well above the value that would result in abnormal bleeding.

*Prothrombin activities* on all cases were within normal limits during the present study. Method used was a modified Quick method based on controls.

TABLE IV

Prothrombin Activity Expressed as Per Cent of Normal Past Hospital Admissions May 1947

	4-14-41	7-19-46	
Case 2			100%
3			150
6			150
9		70%	90
12	56%		90

Tourniquet tests were carried out in the following manner. A blood pressure cuff was maintained half way between systolic and diastolic pressures for 15 minutes, and the petechiae were counted in a circle one-inch in diameter on the flexor surface of the forearm. More than 10 new petechiae were considered a positive test. Only Case 2, the 77-year-old individual, showed a positive test. Examination of his fundi revealed marked arteriosclerotic retinopathy.

Serum calcium determinations were done on Cases 6 and 12. The value for both was 9.4 mg. per cent.

Clot retraction began within one hour and was completed well within 24 hours in all cases.

The following table contains the results of tests carried out on relatives of the five clinical "bleeders." The exact family relationship may be found by referring to chart 1.

May 1947

	Coagulation Time	Clot Retraction	Bleeding Time	Platelet Count	Tourniquet Test	Prothrombin Activity
Case 1	7½ minutes	Normal	5 minutes	—	—	
4	4 minutes	Normal	3½ minutes	230,000	Negative	120% of normal
5	4½ minutes	Normal	4 minutes	—	—	
7	3½ minutes	Normal	2½ minutes	188,000	Negative	
10	6 minutes	Normal	7½ minutes	530,000	Negative	120%
13	3½ minutes	Normal	4½ minutes	142,000	Negative	160%

It is of interest to note that Case 10 had a definite prolongation of bleeding time. This case is a male, age 9, brother of Case 9, a severe bleeder. He has exhibited no abnormal bleeding.

### DISCUSSION

The symptoms exhibited by these five cases include excessive bleeding from minor cuts, epistaxis, hemarthrosis, postoperative hemorrhage and bleeding from dental sockets after dental extractions. No history of petechiae was discovered although ecchymoses were common. As no female in this family experienced abnormal bleeding, no excessive uterine hemorrhage was encountered. Case 4 and Case 7, both mothers of males with pseudo-hemophilia, have undergone major operations without excessive hemorrhage.

The bleeding time was prolonged in four of the five cases with bleeding tendencies. Case 2, the 77-year-old male, who for the past 20 years had had no tendency toward abnormal hemorrhage, had a normal bleeding time. The prolongation of the bleeding time was extremely variable, at one time being greatly prolonged and at other times being slightly increased or normal. It appears that there is not a direct relationship between the severity of bleeding and the bleeding time, for on one occasion Case 12 was exhibiting severe bleeding when the bleeding time was a high normal. The coagulation time, prothrombin activity and tourniquet tests were within normal limits during present study.

The diagnosis of pseudohemophilia is not difficult. The discovery of signs of abnormal clinical bleeding in the presence of a prolonged bleeding time with normal platelets and normal coagulation time would indicate pseudohemophilia. There is commonly a family history of the disease, although this is not always present. As pointed out by Estren, Mēdal and Dameshek,<sup>1</sup> there is some variability in the result of the tourniquet test, prothrombin activity and clot retraction. Clot retraction and prothrombin activity are usually within normal limits. The tourniquet test was positive in 50 per cent of the cases reviewed by these authors. Either sex transmits the disease. Either male or female may be afflicted, although in this present study only males were involved. The high incidence in males and the tendency for the symptoms of bleeding to decrease with age has been described by other authors.<sup>3, 4, 5</sup>

*Therapy.* Pressure dressings, local thrombin,\* thromboplastin,† calcium, vitamin C, hykinone,‡ oxycel,§ tannic acid packs, snake venom, intramuscular whole blood, citrated blood transfusions, and direct whole blood transfusion have all been used in an effort to halt bleeding. All appear to have had no effect with the exception of pressure dressings and direct whole blood transfusions. Citrated blood has had no effect in causing cessation of bleeding, but both Case 6 and Case 12 have had abrupt cessation of bleeding following direct blood transfusions. Case 9, who was under observation in the hospital during this present study, received a direct transfusion prior to debridement and removal of granulation tissue of a scalp wound which had been packed with gauze. Unfortunately, a bleeding time was not done immediately before transfusion; however, nine days previously the bleeding time was greater than 15 minutes. After transfusion, the granulation tissue about the laceration was trimmed without any abnormal bleeding. Post-operatively no hemorrhage was noted and 19 hours later the Duke bleeding time was six minutes. Owing to the tendency of these individuals to exhibit intermittent prolonged bleeding time, no definite conclusion as to the effect of the blood transfusion on the bleeding time can be drawn. Direct blood transfusions appear to have a direct effect on stopping bleeding. Fowler<sup>5</sup> has also found transfusion to be effective.

### SUMMARY

A family with a hemorrhagic tendency has been presented and five of its members have been classified as cases of pseudohemophilia. Case reports of these individuals and the findings of two autopsies on two other members of the family have been reported.

\* Topical Thrombin, Parke Davis Co., Detroit, Michigan.

† Thromboplastin, Lederle Lab., N. Y., N. Y.

‡ Hykinone, Abbott Lab. (Vit. K Prep.), Chicago, Ill.

§ Oxycel, Parke Davis Co., Detroit, Michigan.

The outstanding laboratory finding was a prolonged bleeding time with the remainder of the findings within normal limits.

Therapeutic results with direct blood transfusions are noted as being effective in these cases.

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# EXPERIMENTAL AND CLINICAL THERAPEUTIC STUDIES ON LYMPHOSARCOMA \*

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## INTRODUCTION

IN the entire field of medicine no disorder gives so much concern to physician and layman alike as do the neoplastic diseases of the lymphoid tissue. Of this group, lymphosarcoma is a particularly serious problem. The comparatively intractable nature of the condition, its rapid progress, and the terrifying nature of the associated symptoms, all justify this concern. Especially grave is its tendency to occur in the young.

Lymphosarcoma not only presents a therapeutic problem. It also provides for the investigator particularly fascinating and useful experimental material. The tendency of the lesions to be superficial, subject to direct observation, and the invasive nature of the growth, are important features. The existence of an exact analogue in small animals, a neoplasm which can be induced and also transplanted at will, provides a unique opportunity for research directed toward therapy in man.

Finally, in both the investigative and clinical aspects of lymphosarcoma, real progress has been made. This is of a degree and type which appears to justify detailed review, since it is more apparent, perhaps, than is the case with any other form of neoplasm. Because of this fact the new knowledge concerning lymphosarcoma may well serve as a guide to what progress can be expected with cancer in general in the years to come.

A most serious error is often made in discussing the treatment of cancer. It is to describe an event following the institution of a therapeutic procedure as the result of that procedure. A conclusion of this type is never justified unless adequate data are at hand to prove that a change of the patient's course is one which is not simply a feature of the natural course of the disorder when untreated.

Particularly often in recent months have claims been made for the usefulness of one or the other substance in treating neoplasms. These claims tend to be based on minor changes in the clinical condition of the patient or in the appearance of the growth. Control observations frequently are not presented in support. Very often, indeed, careful objective studies of the day-to-day changes in the patient or in the tumor are not available during a pre-treatment period. Only when a clinical trial is under way are measurements or biopsies made. To the great surprise and gratification of the observer, periods of improvement ensue. Perhaps if the growth is biopsied areas of necrosis are seen. If biochemical measurements are made extraordinary day-to-day changes may be recorded.<sup>1,2</sup>

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When the time comes to cast up accounts to evaluate these changes it is usually found that the same variations in course occur under any therapeutic régime or none at all.

With the importance of spontaneous changes of course in mind, it is well to renew the natural history of lymphosarcoma.

It would be well if every physician concerned with lymphosarcoma were to read the original description by Kundrat.<sup>3</sup> This is advocated because he faced the same problems of differentiating the disease from other neoplasms involving lymph nodes as are faced by every practitioner in making a differential diagnosis of a mass in neck or groin.

Further, Kundrat made the key observation which should be the cornerstone of any therapeutic attack. This was that from time to time only a single site of origin could be found. This concept of the unicentric origin is as important to the clinician as any other single consideration of lymphosarcoma.

Too frequently the true neoplastic nature of the enlarged lymph node is forgotten until control is impossible. If not forgotten, too often it is assumed to be metastatic from a primary epithelial neoplasm.

The evidence for a unicentric origin in at least some instances of lymphosarcoma is excellent, indeed unequivocal. It is found in the very substantial number of instances in which a primary focus of characteristic structure is removed surgically or destroyed by radiologic means with complete permanent cure.

Hellwig<sup>4</sup> reports that 21 of his 234 cases of malignant lymphoma showed only a single primary focus. Gall<sup>5</sup> reported almost the same incidence—10 per cent of 135 autopsied cases. Of 33 patients with gastrointestinal lymphosarcoma, only four could be shown to have metastasized to the regional lymph nodes. Furthermore, of 16 instances in which the regional nodes appeared to be involved on gross examination, only hyperplasia could be found on microscopic study. This observation is perhaps of particular importance since it indicates that many instances may exist in which an attempt at resection may be justified even though inspection of the tissue may suggest that extension has taken place.

These results are sometimes explained on the grounds that erroneous histologic diagnoses of lymphoid neoplasms are frequently made, due to the unsatisfactory nature of the morphologic criteria. It is difficult to believe, however, that these factors can obtain in every reported instance of cure. It is far easier and more logical to hold that the disorder does arise regularly in a single cell or cell group but often has extended before the primary locus is recognized. Any worker with transplantable lymphosarcoma in animals cannot fail to be impressed with the fact that however carefully one localizes the implanted fragment of tumor, migration to local nodes and systemic progression occur with dramatic speed.

This tendency of a disease to become systemic should not blind the observer to the possibility of localization, however. It is extraordinary how

often this is forgotten and how disastrous this may be to the patient since the really brilliant, life-saving results are obtained either by radiation or by surgery in the unicentric form of the disorder.

The age and sex distribution of lymphosarcoma has been referred to frequently in the classic publications on the subject. They deserve repetition here, however, with consideration of the possible meaning of these factors in terms of etiology of the disease.

It is interesting that in an early publication of Jackson's<sup>6</sup> he states that virtually no case of lymphosarcoma occurred in the first, third, fourth, or fifth decade. The report by Sugarbaker and Craver<sup>7</sup> describes a uniform distribution by decades and states that the disease is rare before the age of 20. It is apparent that age distribution may vary significantly with the institution involved, and unless some pains are taken to control this factor misleading figures may be obtained.

When the later figures of Jackson<sup>8</sup> are contrasted with similar ones pertaining to other forms of neoplasms a pronounced contrast is seen. In few other conditions is there such a sharp limitation of incidence to childhood, adolescence and late puberty. In no other does adult life almost seem to interdict the occurrence of a particular neoplasm.

Less pronounced, but very definite, is the predominance of lymphosarcoma in males.

These have been the findings of practically every investigator who has compiled statistics on the incidence of lymphosarcoma. Allowing for the minor statistical errors the disease is certainly twice as frequent in males as in females.

To draw any conclusion from these facts is, of course, impossible. One can speculate, however, and thereby derive some discussion if no decision.

It is obvious to any anatomist that a disorder which is predominant in one sex and is practically confined to childhood must have something to do with those chemicals which control sex and maturation. I refer, of course, to the substances secreted by the glands of internal secretion, the protein hormones of the pituitary and the steroids of gonads and adrenals. It is not surprising, therefore, that in certain strains of experimental animals, as shown by Gardner,<sup>9</sup> true neoplasms of lymphoid tissue can be caused to occur regularly by the administration of at least one steroid hormone, estradiol.

It is odd that more attention has not been given to the untreated course of lymphosarcoma. The reason is, of course, apparent; a therapeutic procedure of some effectiveness, x-radiation, was at hand before detailed knowledge of the natural progress was realized to be important. Enough observations are at hand, however, in clinics with adequate experience to suggest that the disease is not one marked wholly by an unchanging march toward fatality. Indeed, it will be seen, if objective criteria are applied, that minor variations in progress are the rule rather than the exception, though spontaneous remission is not nearly as marked a feature as it is in lymphatic leukemia.

When lymphosarcoma has progressed to the stage of widespread dissemination, so-called lympholeukosarcoma, the outlook is of course poor. Even at this stage evidence of irregular regression can be found; insofar, at least, as the size of lymph nodes, the extent of secondary manifestations and the degree of lymphocytosis are concerned.

The cause of these remissions, or periods of temporary improvement, is wholly unclear. There seems to be little doubt that some have occurred following infectious disorders of varied bacterial etiologies. Indeed, nearly every clinic has a record of at least one patient who was thought to be moribund, in whom some type of infection supervened and a dramatic, in some instances complete, though temporary, regression set in.

Obviously, when this sort of change can occur, even though rarely, in the untreated patient, its possibility must be considered when any therapeutic régime is instituted.

In a very large proportion of the patients with lymphosarcoma the disease arises primarily in lymph nodes. It is probable, according to Craver,<sup>7</sup> that more than 60 per cent of the patients never show evidence of an extranodal primary lesion. Where an extranodal primary lesion is present, it is almost always in the structures of the head and neck, tonsils or naso-pharynx. Most of the remaining cases are primary in the gastrointestinal tract, with rare disease in lung, bone and skin.

### SURGICAL THERAPY

Regularly, when the treatment of lymphosarcoma and of Hodgkin's disease is discussed, the fact is rediscovered or at least reannounced, that surgical resection of localized disease has cured a certain number of patients. Reference to this fact is made here only for the sake of completeness and to maintain an awareness of its existence. The possibility should be borne in mind that perhaps the predominance of disseminated lymphosarcoma may lead to the acceptance of routine radiation therapy whenever the histologic diagnosis is made. This may be done without an adequate attempt to establish the disorder as a localized one. It is conceivable, furthermore, on the basis of experimental evidence, that involvement of regional nodes accessible to removal may not rule out the possibility of surgical cure. It is interesting to note how infrequently surgery is given serious consideration even in clinics where its potential value is thoroughly understood.

The practical value of surgical therapy is best established perhaps by the figures of Hellwig.<sup>4</sup> Of 234 patients, he treated 130 by surgery with post-operative irradiation. A five-year survival rate of 24.6 per cent is reported. Of 21 patients with a single focus of disease so treated, 12, or over 50 per cent, were well for over five years. This is in striking contrast to the survival figure of roughly 10 per cent given for radiation therapy of all patients and an average duration of 20 months. A similar case for surgery has been made by Gall.<sup>5</sup>

It is interesting that in the face of this evidence, Stout<sup>10</sup> sees no reason to prefer surgical excision.

### RADIATION THERAPY

This topic has been discussed so exhaustively by so many authorities of great experience, that it warrants only brief mention here. There can be no question from the evidence that cures have been obtained by this means. It is probable that some increase in the number of cures can be expected with increasing diagnostic acumen, technical skill and experience.

From the evidence at hand it appears that in the instances in which cures by radiation have been obtained, the disease has been rather well localized. This raises the question, of course, of whether surgery would not have been equally or perhaps more effective.

Palliative treatment by irradiation also is so well established as to justify little discussion. Here again one principle has been clearly defined by clinical experience. This is that the degree of palliation obtained by therapy is almost exactly a factor of the extent of disease. If it is localized to an organ, or area of well-defined extent, sufficient radiation can be delivered to the neoplastic tissue to destroy it or halt for a time its growth. If the disease is not localized or its limits cannot be defined the chances are seriously against any profound or prolonged effect of therapy. This simple concept brings the treatment of lymphosarcoma directly in line with that of other neoplasms but with two points of difference. Lymphoid disease has a greater tendency to disseminate early and has a much greater sensitivity to radiation. For the latter reason the possibility of cure by x-rays of deep-seated disease should be distinctly greater for lymphosarcoma than for neoplasms of other tissues. This presumption is probably supported by the clinical results.

Sugarbaker and Craver<sup>7</sup> report a five year survival rate of all cases treated at the Memorial Hospital of 15.9 per cent, and apparent cures 10.6 per cent. This compares well with the figures published from other clinics using radiation therapeutically.

An interesting point in a consideration of end results is the fact that the giant follicle lymphomas show an average survival rate of 42 months, whereas the patients with malignant lymphocytoma survive an average of 18.6 months.

It is important to note that of the 21 patients surviving only four had two contiguous areas of involved tissue when first seen. This bears out the contention specified previously, that local disease is curable and generalized disease is not.

Age plays an important rôle in prognosis. Of Sugarbaker's<sup>7</sup> series, only one patient under the age of 30 survived, and the life expectancy in this group was half that among older patients.

TREATMENT BY  $P^{32}$ 

The announcement by Lawrence <sup>11</sup> of the use of radioactive phosphorus in the treatment of leukemia was a dramatic one. It stimulated immediately hope that by the use of this isotope control or cure of lymphosarcoma could be obtained. The study by Marinelli <sup>12</sup> of the physical basis of dosimetry in radiation therapy should be consulted on this point. Without perusal of this erudite work, however, a simple examination of the evidence gives reason for skepticism. The figures published by Lawrence <sup>13</sup> for the preferential deposition of  $P^{32}$  in lymphomatous as compared to normal tissue of a similar type are important. The neoplastic cells were found to contain only from two to three times, rarely more, of the isotope than did normal cells.  $P^{32}$  is an emitter of gamma radiation of great penetrating power, hence the destructive effects penetrate a considerable distance. The dose of gamma rays required to destroy the cells of lymphosarcoma is well known. From these facts it is clear that it would be unlikely that one could obtain, with a preferential deposition as low as 2 or 3 to 1, curative concentrations of  $P^{32}$  in the cells of lymphoma without a serious hazard of ruin to the normal hematopoietic tissues.

Actual experience has borne out this assumption, although it must be said that the publication of Kenney and Craver <sup>14</sup> presents surprisingly good evidence of temporary remission in some instances following  $P^{32}$  therapy of lymphosarcoma. Whereas sometimes similar results have been attained in other hands, one is impressed by their rarity. Warren,<sup>15</sup> Reinhard,<sup>16</sup> and many others support the conclusion that  $P^{32}$  is not a useful agent in the treatment of lymphosarcoma and, further, that its employment is associated with an unpredictable hazard.

The possibility of treatment of lymphosarcoma by some form of isotope therapy in the future cannot be ruled out. We know, now, from experience with cancer of the thyroid gland, that preferential deposition of radioactive isotopes in neoplastic as compared to normal tissue may have to attain levels of 50 to 1 or more to effect control of the growth. To do this for lymphosarcoma will require some radically new approach.

## TREATMENT WITH HN2

The extraordinary development of war research which led to a knowledge of the leukotoxic action of the nitrogen mustards represents a landmark in therapeutic approach to neoplastic disease. This statement should not be taken to imply that the  $\beta$ -chloroethylamines are in any sense curative, or indeed that they have any value in treatment beyond the transient and irregular control of neoplasms of the hematopoietic system. Even this control, however, may be a matter of the greatest importance. It establishes beyond question the fact that a chemical treatment of one form of neoplastic disease exists, poor and incomplete though this may be. It is hard to believe that

some modification of the molecule already known to be active will not lead to more effective compounds in the future.

The facts regarding nitrogen mustard can be easily summarized. These compounds are characterized by the presence in their molecule of a  $\beta$ -chloroethyl group. This group in the blood becomes temporarily cyclicized to an imine ring which has, while it exists, a profound leukotoxic activity. The effect is exerted on all hematopoietic tissue including the lymphoid, and is associated with a series of toxic side reactions which may be serious or indeed fatal. Neoplastic cells of origin from hematopoietic tissue share, with their parent normal cells, sensitivity to the toxic effects of the mustard compounds. From the available evidence, indeed, certain neoplastic cells may exceed their normal relatives in sensitivity to these compounds.

The first proof that a nitrogen mustard could be employed effectively in the treatment of lymphoma was advanced by Gilman<sup>17</sup> and his associates. Soon after, Jacobson<sup>18</sup> described pronounced effects upon Hodgkin's disease. Since that time very extensive observations from many clinics have been reported in a number of publications. It suffices to state here that the treatment of lymphosarcoma by the nitrogen mustards has not been very satisfactory. In occasional and unpredictable instances dramatic regressions result. It is safe to state that these are so transient in most cases that the distress caused by the treatment is hardly justified by the benefit obtained. Unfortunately for the rule, however, an occasional patient with generalized lympholeukosarcoma is seen whose improvement is not only impressive but also is of long duration.

It is obvious from what has been said before that localized lymphoid disease is wholly unsuitable for treatment by nitrogen mustard. Only x-rays or surgery should be used. Whereas the chemical can be tried in cases of generalized lymphosarcoma it probably offers little more, if as much as, x-ray therapy. If other means have failed, however, there can be little question but that an adequate course of nitrogen mustard therapy is wholly indicated, and may be transiently life-saving.

#### MISCELLANEOUS THERAPEUTIC PROCEDURES NOT ESTABLISHED BUT UNDER STUDY

Colchicine has been eyed for years as an agent of potential usefulness in the treatment of neoplasms of various types, including lymphosarcoma. The strong effect of this substance in stopping mitosis provides good reason for consideration of its use in restraining growths characterized by more rapid cell division than normal. The fact should be recalled that this is not necessarily true of neoplasms. To date no adequate data exist to justify the clinical use of colchicine or compounds allied to it.

Hahn<sup>19</sup> and his associates have described the preparation and have referred to the use of colloids of radioactive gold and of manganese. The

distribution of the radioactivity resulting from the injection of these materials has been described.

It is entirely reasonable to assume from the data presented by these investigators that a substantial part of the administered colloid is deposited, together with its radioactivity, in phagocytic cells. It is further probable that it remains for a time at least in those phagocytic cells which are in immediate contact with the circulation, the cells of the reticulo-endothelial system. The prominence of this system in those tissues which are subject to invasion by lymphosarcoma renders understandable the assumption that a radioactive element deposited in it would be therapeutically active. This is of course wholly possible, but hardly seems probable. The distribution of phagocytic endothelium is most widespread, particularly so in tissues of vital importance to life and composed of hematopoietic cells which are most sensitive to radiation.

No evidence has been advanced, so far, to warrant the conclusion that radioactive colloids can be controlled sufficiently well in their distribution in the body to be specifically destructive to neoplastic cells.

The discovery by Paterson<sup>20</sup> and her associates of the therapeutic effect of urethane in the treatment of leukemia has aroused much attention. This outstanding work is an example of a model program of medical study. There can be no doubt from the evidence that urethane, in adequate doses, has a distinctly inhibitory effect upon the growth of certain types of neoplastic cells. A particular advantage of this compound, is, of course, the fact that the material is active by mouth.

A number of articles have appeared on the use of urethane in the treatment of leukemia, and one<sup>21</sup> which indicates an effect on cancer of the prostate gland. Whereas attempts have been made to control lymphosarcoma the results have been at best equivocal and at worst unsatisfactory. No proof exists today, in published form, which warrants the belief that urethane or any analogous compound so far prepared is of even potential utility in the control of lymphosarcoma.

An important development has been the study by Shear<sup>22</sup> and his associates of the use of polysaccharide from *Serratia marcescens* culture filtrate. This is, of course, a development of the earlier study by Coley and others of the effect on malignant tumors of a vaccine composed of a mixture of *Streptococcus erysipclatis* and *B. prodigiosus*. This extremely interesting and important study has advanced clear evidence that the polysaccharide has a profound effect in inducing hemorrhage in transplanted tumors and inducing a variable degree of necrosis in spontaneous ones. The pyrogenic effect of the material has been a handicap as far as its general use in man is concerned. It is hoped that studies now in progress will be useful in solving this problem.

The report of Brues and Shear<sup>22</sup> refers to the treatment of one patient with lymphosarcoma by polysaccharide and records are available on others. In Brues' patient several enlarged lymph nodes remote from the site of recent

x-ray therapy were seen to regress and one of the remaining tumors had developed a hemorrhage.

In any general discussion of lymphosarcoma and its therapy some view of the future must be taken. This must include very obviously a consideration of experimental work now in progress or visualized for the near future.

A matter of interest is the study of Kopac.<sup>23</sup> This investigator has employed a complex and delicate physico-chemical procedure to detect substances of potential value to tumor chemotherapy. Observations made by this procedure led in part to the employment of stilbamidine in the treatment of myeloma. No data on its use in lymphosarcoma have appeared so far.

Two studies have been published which suggest that 11-dehydro-17-hydroxycorticosterone (Compound E) have an effect in restraining the growth rate of lymphosarcoma in experimental animals. The observation of Heilman and Kendall<sup>24</sup> was that by the use of this material implantation of a strain of highly malignant tumor cells did not result in the growth of tumors and rapid regression of well developed tumors took place. Considerable variation in the experimental results was observed.

Somewhat similar results were reported by Murphy and Sturm<sup>25a, b</sup> who employed a transplantable tumor of the rat which, depending on the route of inoculation, may present either a lymphosarcoma or leukemia. It is unfortunate that such small amounts of compound E are available as to make large scale repetition of these experimental results not feasible.

The field of anti-vitamins and anti-hormones has been given careful consideration by those interested in the therapy of lymphosarcoma. Only one publication bearing on this area of work has been reported, however. Stoerck<sup>26</sup> has described a failure of a transplantable lymphosarcoma to take in animals deprived of pyridoxine. Further, he was able to cause regression of established transplants of the tumor by administering a pyridoxine antagonist. Further results of this type will be awaited with great interest. Although adequate data are not available today they may be expected in the near future in light of the numerous studies now in progress.

The treatment of lymphosarcoma presents today a curious anomaly. This most radio-sensitive tumor shows, nevertheless, resistance to control by x-radiation in terms of substantial cure rates or prolongation of life. The cells of this neoplasm are so sensitive to a change of environment that almost alone, of all new growths, they cannot be grown in tissue culture or upon the chorioallantoic membrane of the chick. Yet in man they are amazingly resistant to injurious chemicals.

Happily, however, accurate experimental technics have now been developed and are in extensive employment. A number of chemical compounds are at hand which injure lymphosarcoma cells in animals and with some degree of preferential specificity.

It would be remarkable if, in view of the effort now under way, major progress were not made in the future.



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# ABNORMAL RAPID RHYTHMS ASSOCIATED WITH DIGITOXIN THERAPY \*

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SEVEN patients developed abnormal rapid cardiac rhythms (idio-ventricular rhythms, paroxysmal ventricular tachycardia or interference and dissociation) during a recent fifteen and one-half month experience with digitoxin at the Peter Bent Brigham Hospital. Because they seemed more frequent and insidious than with digitalis leaf the incidence and manner of these toxic reactions were studied in this group and in a comparable group which had received digitalis leaf.

From February 1, 1943 through May 31, 1945 inclusive, 5,082 patients were treated in the Medical Service. Of this group, 940 (or 18.5 per cent) had heart disease. In the vast majority (15.5 per cent) the cardiac condition was the reason for the patient's hospitalization, whereas in a small group (3.0 per cent) the cardiac condition was of secondary importance and not the actual occasion for the patient's hospitalization. Of this group of 940 cardiacs, 534 patients (56.5 per cent of the cardiacs or 10.5 per cent of all medical admissions) were treated with pills of the powdered digitalis leaf. Most of these treated cardiacs (6 per cent of the entire group) received digitalis in "priming" digitalizing doses, while a smaller number (4.5 per cent) were given maintenance doses only, usually one tenth of a gram daily.

During this "digitalis leaf period," although 15 patients had abnormal rhythms of the type under discussion (six paroxysmal ventricular tachycardia, five paroxysmal nodal (?) tachycardia, two paroxysmal tachycardia of undetermined type, and two idioventricular rhythms) 10 occurred in patients not receiving digitalis and there were only two in which the tachycardia could certainly be attributed to digitalis intoxication. One was a 47 year old negress with malignant hypertension, uremia, and pulmonary embolism who had been on maintenance doses of digitalis leaf and then developed an idioventricular rhythm (rate 110) when given 0.1 gram digitalis leaf daily for 18 days. The other was a 62 year old man with idioventricular rhythm (rate 136) to whom digitalis had been given in rather large doses (0.7 gram of the leaf in two days) after being on maintenance doses of digitalis leaf for months in face of desperate, grave congestive heart failure. In three additional cases (two paroxysmal ventricular tachycardia and one atypical paroxysmal tachycardia), although the patients had received digitalis, the rôle of digitalis in the inception of these rapid rhythms was very

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questionable. However, for the sake of the argument, all five of these cases are here considered as due to digitalis intoxication.

From January 1, 1946 through April 15, 1947, on the other hand, when a large scale clinical trial of digitoxin had been begun, there were 2,816 medical admissions. During this "digitoxin period" 338 patients (12 per cent of the medical admissions) received digitoxin in therapeutic or therapeutic plus maintenance dosage. During that period, seven cases of toxic rapid action of the heart were encountered. The attending resident and visiting physicians, under whose direction the drugs were given, were essentially the same in each period and the same degree of care and caution was exercised in the administration of each preparation. Most of the subjects, being hospital patients, had severe or moderately severe congestive heart failure, else, particularly at this time, they would not have been hospitalized. One might question whether a group of non-hospitalized patients in milder failure would have shown as high an incidence of toxic reactions.

With the exception of the relative infrequency of nausea and vomiting, the American literature to date on the digitalis glycoside, digitoxin, has had remarkably little to say about the incidence of other evidences of toxicity.\* It is therefore of considerable interest to report these seven cases in some detail.

*Case 1.* A 46 year old electrical supervisor with rheumatic heart disease, mitral stenosis and insufficiency was admitted to the Peter Bent Brigham Hospital in January 1946 in severe congestive heart failure. Five months before the present admission, he had been treated there because of congestive failure. After receiving 40 cat units of digalen during a 20 day period an attempt was made to lower his apical rate below 80 to 85. To this end he was given digitoxin in the dosage of 0.3, 0.2, 0.4, 0.6, 0.6, 0.8, and 0.2 milligram on seven successive days. At the end of that time digitoxin was stopped because of nausea and vomiting but no unusual tachycardia or ectopic rhythm developed, the apical rhythm remaining in the 80's and the rhythm grossly irregular. He was discharged in good compensation taking 0.2 gram digitalis leaf daily.

Three weeks before his second admission, following a respiratory illness, digitalis was discontinued because of the development of anorexia. A week later digitalis was started again but his symptoms of congestive failure became worse. Five days before admission, he was started on digitoxin, receiving 0.4 milligram daily for two days followed by 0.2 milligram daily for three days. In spite of this his edema increased and his heart rate rose to 120.

Physical examination showed periods of rapid, totally irregular rhythm alternating with bigeminy and bursts of rapid rhythm. Electrocardiograms (figure 1A) showed auricular fibrillation, right axis deviation and premature ventricular beats with bigeminy. In Lead I these were uni-focal but in Lead III they were bi-focal. In Lead CF<sub>2</sub> there was a bidirectional ventricular tachycardia with a rate of 164 beats to the minute, but in the other precordial leads the rhythm was bigeminal. With this evidence of digitalis toxicity digitoxin was discontinued. In a second electrocardiogram taken later that day (figure 1B) three distinct rhythms were

\* In a publication appearing since the present paper was written, Master [MASTER, A. M.: Digitoxin intoxication. *Jr. Am. Med. Assoc.*, 1948, cxxxvii, 531] warns that the administration of digitoxin, like that of any other preparation of digitalis, because of the variability in absorption, excretion and therapeutic effect, is an individual experiment.

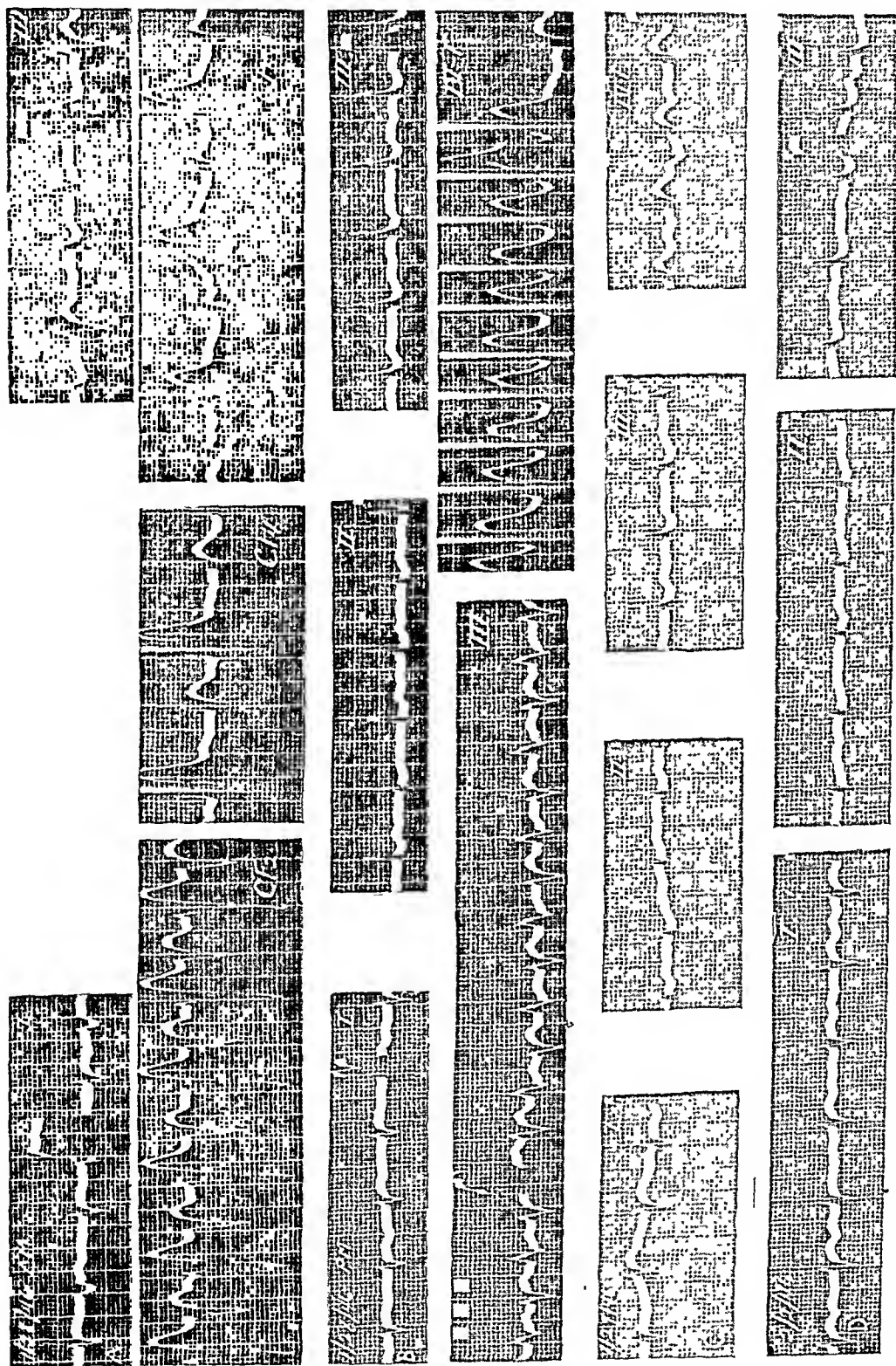


FIG. 1. (Explanation of figure on opposite page.)

recorded. The standard leads showed an idioventricular rhythm with a rate of 104 beats to the minute. Later a bidirectional ventricular tachycardia was seen in Lead III. The rate during this paroxysm was 170 beats to the minute and the rhythm was regular. In Lead IVF a unidirectional paroxysm of ventricular tachycardia was recorded with slight variations in the rate and in the form of the individual ventricular complexes and followed after a compensatory pause by a ventricular complex normal to that lead. The patient was then maintained on quinidine sulfate, 0.2 gram four times daily, for five days.

On the second hospital day (figure 1C) a constant idioventricular rhythm was superimposed on the auricular fibrillation, but there were neither ventricular premature beats nor ventricular tachycardia. The ventricular rate was 108 beats to the minute. On February 2 (figure 1D) auricular fibrillation was recorded as the only arrhythmia with a ventricular rate of 115 beats to the minute.

In spite of these evidences of decreasing toxicity the patient died very badly and died on the ninth hospital day of acute cor pulmonale. Postmortem examination showed infarction of the right lower lobe, right auricular thrombosis and fish-mouth mitral valves.

*Case 2.* A 59 year old white farmer with hypertensive heart disease and auricular fibrillation, having received digitoxin 0.1 milligram during the preceding six days, was admitted to the Peter Bent Brigham Hospital on October 2, 1946 for the purpose of reverting his heart to normal sinus rhythm and thus to decrease the size of a possibly dilated heart. On admission the rhythm was grossly irregular, the rate 80, but at times the rhythm was regular and at other times coupled. During the first four days he was given digitoxin 0.1 milligram daily without developing gastrointestinal or visual symptoms, but this was discontinued on October 5 when the electrocardiograms showed an abnormal rapid rhythm (figure 2) probably ventricular tachycardia. The heart rate was 152 and the QRS interval 0.13 second. On withholding digitoxin the ventricular tachycardia disappeared to be replaced by the underlying auricular fibrillation. After three days on digitalis leaf, 0.1 gram daily, electrocardiograms showed slowing of the ventricular rate to 72, QRS interval 0.1 second, and there were no premature beats. Accordingly on October 18 he was discharged to the care of his local physician on maintenance doses of digitalis leaf.

*Case 3.* A 47 year old housewife with rheumatic heart disease, mitral stenosis and insufficiency, developed auricular fibrillation about three weeks before admission. Because of this she was given 1.2 milligram of digitoxin on the third day before admission, 0.8 milligram two days before admission, and 0.2 milligram on the day before admission. Two nights before admission she became nauseated, on the following day she vomited and that evening she developed diarrhea. She noted no visual difficulties.

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FIG. 1. *Case 1.* Rheumatic heart disease with mild uremia and congestive heart failure. No tendency to tachycardia from 3.1 milligrams digitoxin over seven day period at previous admission. During five days preceding present admission received 1.4 mg. digitoxin without developing gastrointestinal symptoms.

A. Electrocardiograms on admission show auricular fibrillation, right axis deviation, and bigeminal rhythm in Leads I and III and  $CF_1$  and  $CF_2$  with a paroxysm of bidirectional ventricular tachycardia recorded in Lead  $CF_2$ .

B. Tracings later that day show: (1) idioventricular rhythm, rate 104 in the conventional leads; (2) bidirectional ventricular tachycardia later in Lead III, the individual ventricular complexes corresponding in form to the premature ventricular beats seen earlier in the day in Lead III (complexes 2 and 4 of the right upper tracing); and (3) classical unidirectional paroxysmal tachycardia in Lead IVF.

C. Second hospital day. Constant idioventricular rhythm superimposed on auricular fibrillation. No ventricular premature beats or ventricular tachycardia.

D. Sixth hospital day. Auricular fibrillation as only arrhythmia. Recovered from digitoxin intoxication on withholding drug but died of pulmonary infarction.

Physical examination on the day of admission, February 3, 1946, showed the heart to be regular and the apical rate to be 140 beats to the minute.

Electrocardiograms (figure 3) showed auricular fibrillation and an idioventricular rhythm, the rhythm being regular and the ventricular rate 140 beats to the minute. The ST segments in Leads II and IVF (the latter not shown in the tracings reproduced) were cupped and depressed and  $T_a$  was inverted.

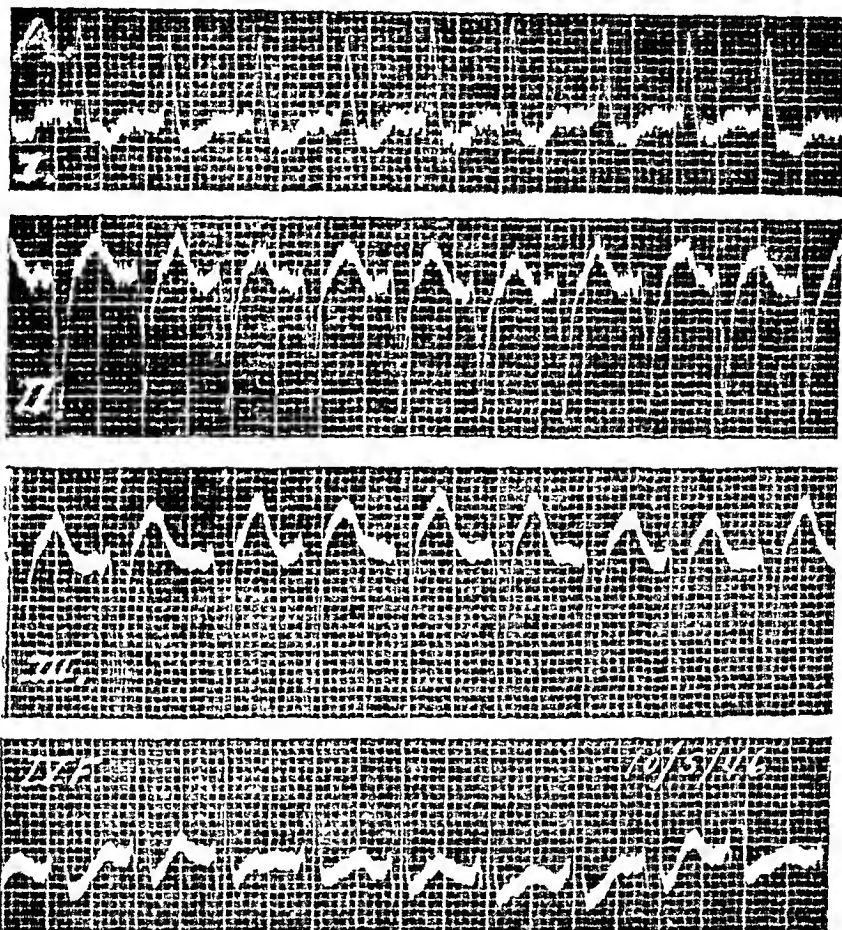


FIG. 2. Case 2. Hypertensive heart disease with congestive heart failure. Received 0.1 mg. digitoxin daily for 10 days. No gastrointestinal symptoms.

Third hospital day. Ventricular tachycardia, rate 152, QRS interval 0.13 second. Note very slight irregularity in ventricular rhythm and very slight differences in the appearance of the ventricular complex from cycle to cycle. Ventricular tachycardia disappeared on withholding digitoxin.

Digitalis was withheld until February 3 when the heart had slowed to 90 beats to the minute and had become grossly irregular. On that day she was given 0.3 gram digitalis leaves, on the ninth 0.2 gram, on the tenth 0.3 gram, on the eleventh 0.2 gram, and on the twelfth 0.2 gram. Electrocardiograms at that time showed auricular fibrillation with a ventricular rate of 78. Digitalis leaf was continued 0.3 gram February 13, and 0.1 gram on February 14, 16, and 18, the interval being lengthened because of the re-development of vomiting on February 15. She subsequently reverted to normal rhythm on quinidine therapy. On March 2 she was discharged to the care of her local physician in good condition with no medication. Here then was a patient with a toxic rhythm which subsided on cessation of digitoxin



therapy, following which she was able to take full doses of digitalis leaves with the customary slowing of the ventricular rate.

*Case 4.* A 77 year old Swedish spinster with hypertensive heart disease, chronic nephritis and auricular fibrillation, was admitted to the Peter Bent Brigham Hospital on February 20, 1946 in cardiac failure and uremia. She had received digitalis leaf 0.2 gram daily for the three days preceding admission.

Examination on admission showed a malnourished elderly lady with an apical heart rate of 108, moderate ankle edema and clear lung bases. Electrocardiograms on admission (figure 5A) showed auricular fibrillation, ventricular rate 98, flat T<sub>1</sub>, and left axis deviation.

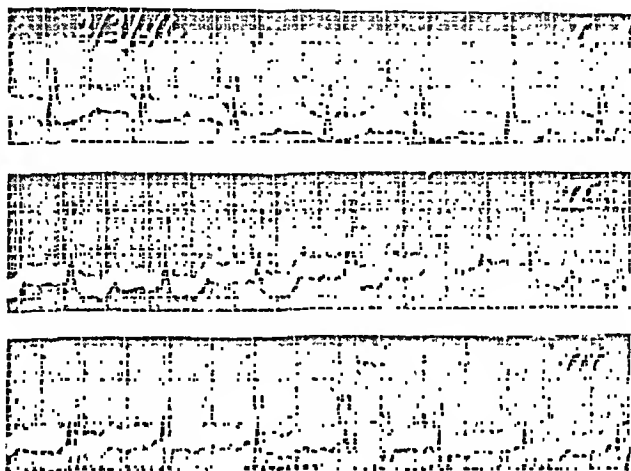


FIG. 3. *Case 3.* Rheumatic heart disease with auricular fibrillation of recent onset. Patient received 2.2 mg. digitoxin over a three day period and developed nausea, vomiting, diarrhea and tachycardia.

Day of admission. Auricular fibrillation and idioventricular rhythm, ventricular rate 140. On withholding digitoxin for five days heart slowed to 90 and became grossly irregular.

Patient subsequently received 1.2 gm. digitalis leaf over five day period. Reverted to sinus rhythm following quinidine therapy disclosing second degree auriculoventricular heart block.

The patient was given digitoxin in the following daily dosage: 0.4 milligram, 0.2 milligram, 0.4 milligram, 0.4 milligram, 0.2 milligram, and 0.2 milligram without developing gastrointestinal or visual symptoms. On the sixth hospital day the pulse rate was found to be 110 and the rhythm regular; the drug was stopped. Electrocardiograms (figure 5B), February 25, 1946, showed auricular fibrillation with idioventricular rhythm, rate 130. Later that evening the same cardiac mechanism was present with heart rate 160 (figure 5C). She died on the following morning. Permission for postmortem examination was not obtained.

It is worthy of comment that from the date of admission to the sixth hospital day the ward officer's notes contained no comment on the heart rate. Yet the nurses' clinical chart (figure 4) showed a radial rate of 112 on the second, 110 on the fourth, and 112 on the fifth hospital day. From the ward officer's notes it seems that this tachycardia was attributed to thyrotoxicosis but the conclusion seems inescapable that if these findings had received the attention they deserved, the drug might have been discontinued at a more opportune time.

*Case 5.* A 41 year old housewife with rheumatic heart disease, mitral stenosis and insufficiency, auricular fibrillation and mild renal impairment, was first admitted to the Peter Bent Brigham Hospital because of congestive heart failure. On the usual methods of depletion compensation was restored. On the seventh hospital day



she was started on digitoxin 0.1 milligram daily and this was later increased to 0.2 milligram daily. Following discharge she was treated by her local physician with digitoxin 0.2 milligram daily.

Following a week of recurrent congestive failure she was readmitted on August 4, 1946. During the five days preceding this admission she had taken 1.6 milligram

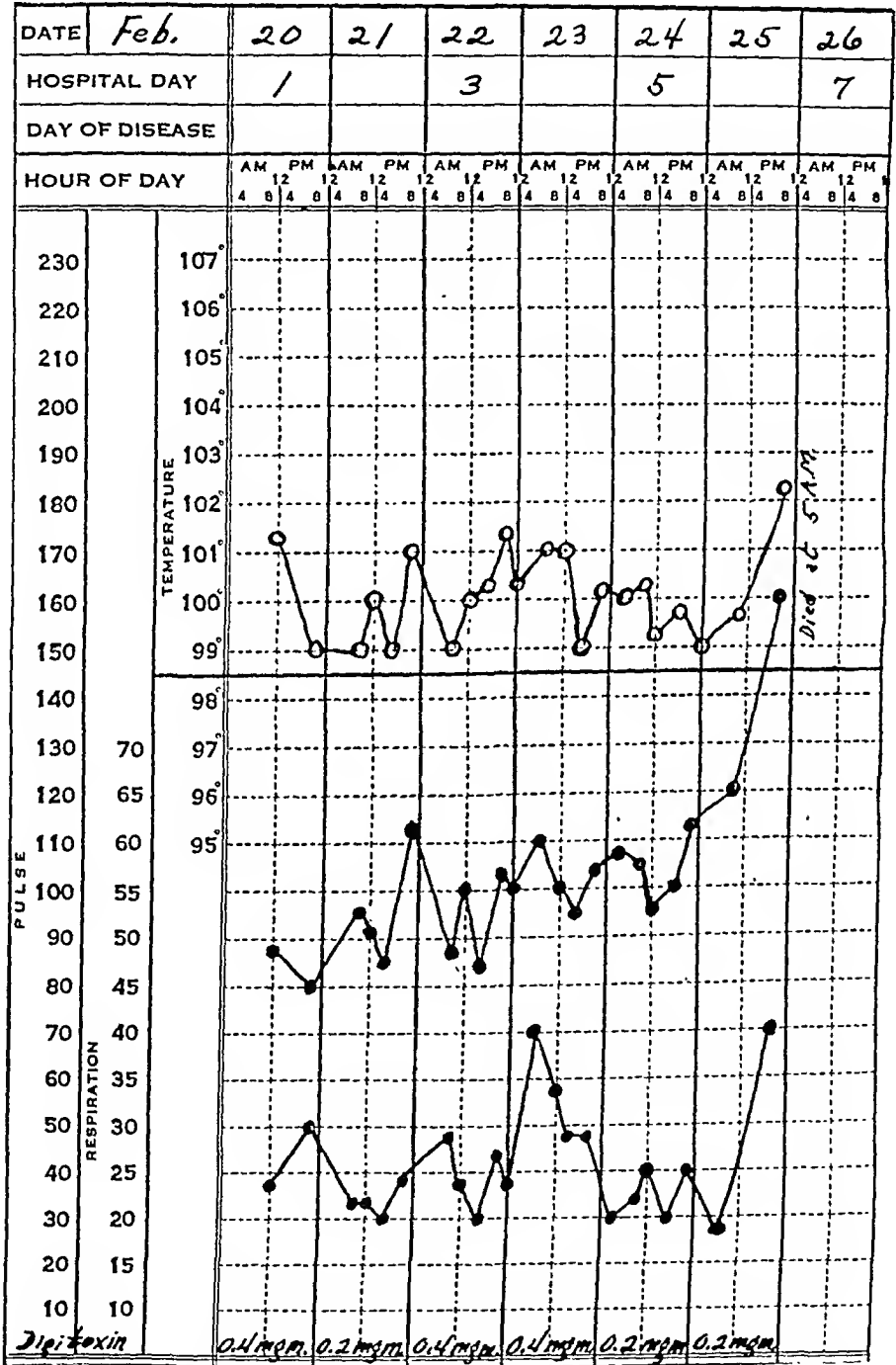


FIG. 4. Case 4. Nurse's clinical chart in case of hypertensive heart disease with auricular fibrillation and uremia, showing schedule of digitoxin dosage and recording of tachycardia days before first mentioned by physician on sixth hospital day.

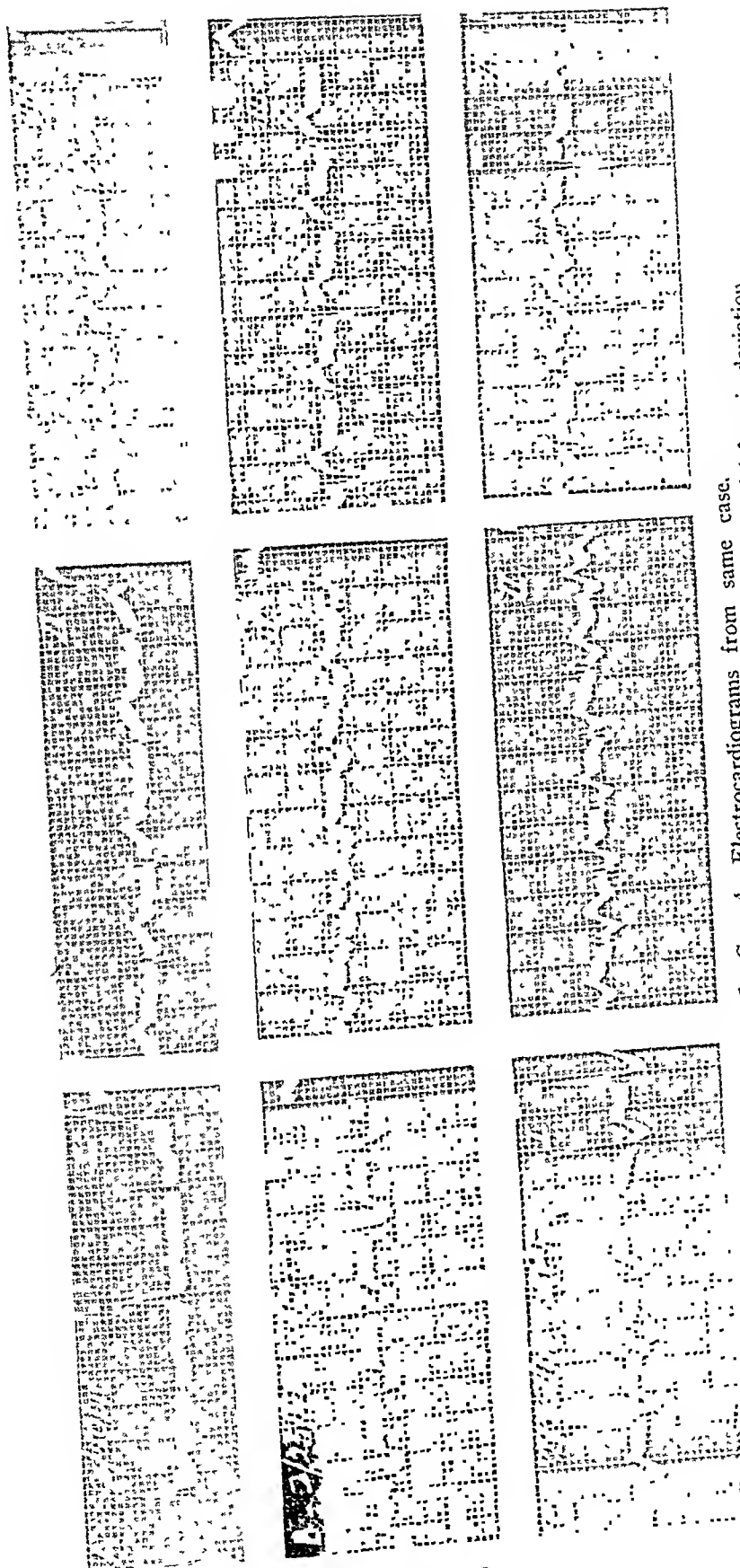


FIG. 5. Case 4. Electrocardiograms from same case.

A. Tracings taken on admission showing auricular fibrillation, ventricular rate 98, flat T, and left axis deviation.

B. Sixth hospital day at 1 p.m. Auricular fibrillation with idioventricular rhythm. Ventricular rate 130.

C. That evening at 6 p.m. Same mechanism. Ventricular rate 160. Patient died following morning.

digitoxin but did not develop nausea, vomiting, or diarrhea. On admission the patient was in severe congestive failure with the signs of shock. A leathery friction rub was heard in the right interscapular area. The apical heart rate was 120 beats to the minute and the rhythm coupled.

Electrocardiograms on the second hospital day showed auricular fibrillation, ventricular premature beats, and a ventricular rate of 92. Despite intensive therapy her condition deteriorated rapidly. On the fifth hospital day her pulse had climbed to 130 and she was given 0.2 milligram of digitoxin by mouth, and on the following day 0.4 milligram intravenously. Electrocardiograms August 11, 1946, showed coupled rhythm with a ventricular rate of 114. At 10 a.m. that morning she was given 0.2 milligram of digitoxin. Later that day the heart rate rose to 140. Electrocardiograms (figure 6) showed paroxysmal ventricular tachycardia. Despite 0.5 gram potassium chloride given intravenously the patient died later that day. Permission for postmortem examination was not obtained.

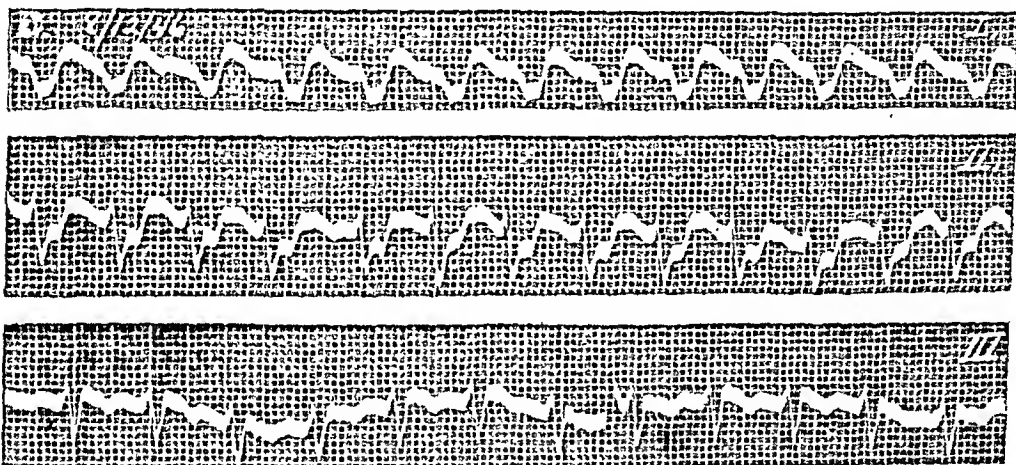


FIG. 6. *Case 5.* Rheumatic heart disease with congestive heart failure, mild pre-renal azotemia and probable pulmonary embolism, apparently already adequately digitalized with digitoxin, then received 1.6 mg. digitoxin during the five days before admission. No gastrointestinal symptoms. On second hospital day electrocardiograms showed auricular fibrillation, ventricular premature beats, right axis deviation with ventricular rate 92. On seventh hospital day bigeminal rhythm was recorded with ventricular rate 114. Another 0.6 mg. digitoxin had been given in desperation in preceding two days. Tracing reproduced was taken on the eighth hospital day. Received additional 0.2 mg. digitoxin as last resort. Terminal ventricular tachycardia.

*Case 6.* A 79 year old retired French-Canadian carpenter with angina pectoris, an old myocardial infarct and chronic auricular fibrillation was admitted to the Peter Bent Brigham Hospital on April 3, 1947 because of congestive heart failure. For several months he had received digitoxin in doses of 0.2 milligram daily.

Electrocardiograms taken on April 4 showed auricular fibrillation, rate 87 beats to the minute, abnormal form of ventricular complex ( $T_{1-5}$  flat) and ventricular premature beats. Accordingly digitoxin, which had been withheld on April 3, was given in dosage of 0.3 milligram on April 4 and 0.1 milligram on April 5. On that date the rhythm as determined at the cardiac apex was, with the exception of a rare ventricular premature beat, quite regular. The patient had not developed gastrointestinal or visual symptoms. Electrocardiograms (figure 7) showed an idioventricular rhythm, rate 108, with rare ventricular premature beats. The ventricular complexes showed QRS intervals measuring 0.18 second in duration and otherwise resembled the typical appearance of left bundle branch block but that diagnosis could not defi-

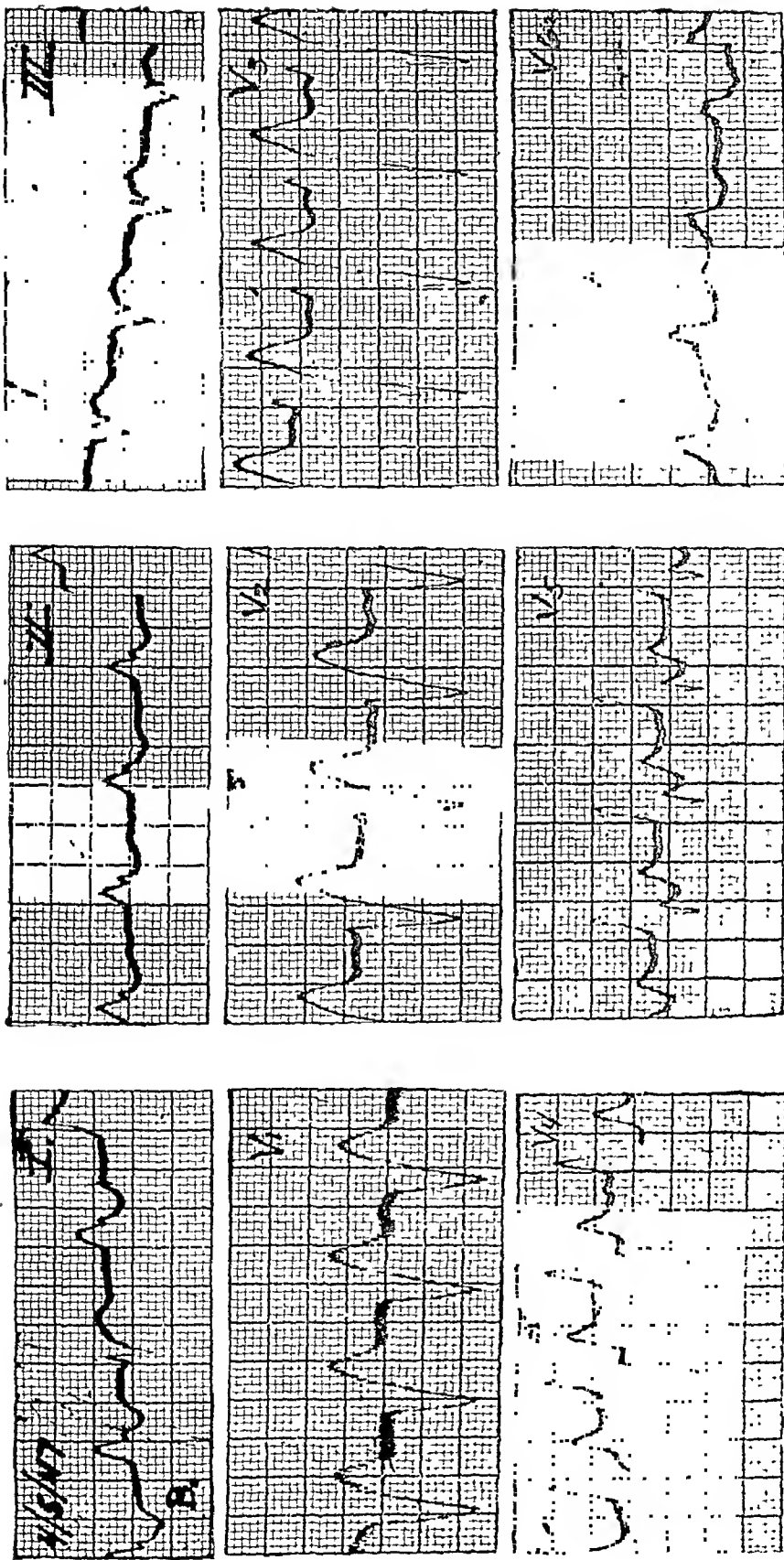


FIG. 7. Case 6. Angina pectoris and old myocardial infarct with congestive heart failure. No renal impairment. Maintenance doses of 0.2 mg. digitoxin daily for several months followed by omission of drug for one day. On the second hospital day electrocardiograms showed auricular fibrillation, abnormal form of ventricular complex ( $T_{1-3}$  flat) and ventricular premature beats. Ventricular rate 87. Patient given 0.3 mg. digitoxin later that day and 0.1 mg. on the following morning. No gastrointestinal symptoms. Tracing reproduced obtained on third hospital day showing transient idioventricular rhythm with pace-maker below the bifurcation of the common auriculoventricular bundle. Auricular fibrillation. Ventricular rate 108. Digitoxin withheld. Regular rhythm lasted four hours. No recurrence of idioventricular rhythm on subsequent maintenance doses of 0.1 mg. digitoxin daily.

nately be made because of the presence of auricular fibrillation. Digitoxin was discontinued. This regular rhythm persisted for four hours at a rate of about 100 when the rhythm reverted to auricular fibrillation with the apical rate 72 and the radial rate 52 beats to the minute. Two days later, the idioventricular rhythm having failed to reappear, repeat electrocardiograms were made and showed auricular fibrillation, premature ventricular beats, QRS interval 0.11 second, and ventricular rate 84. On the following day digitoxin was resumed in the dosage of 0.1 milligram every other day, and on April 20 this dosage was increased to 0.1 milligram daily. Following the resumption of digitoxin the patient showed an excellent diuresis, losing 12 kilograms in weight, and subsequent electrocardiograms showed persistent auricular fibrillation without premature beats but with intraventricular block (QRS interval 0.11 second).

*Case 7.* A 58 year old judge with malignant hypertension, hypertensive heart disease, and myocardial failure in mild uremia, had been receiving digitalis for three years. For two or three months, the patient was not quite certain just how long, he had been taking digitoxin in daily doses of 0.4 milligram. Beginning about three

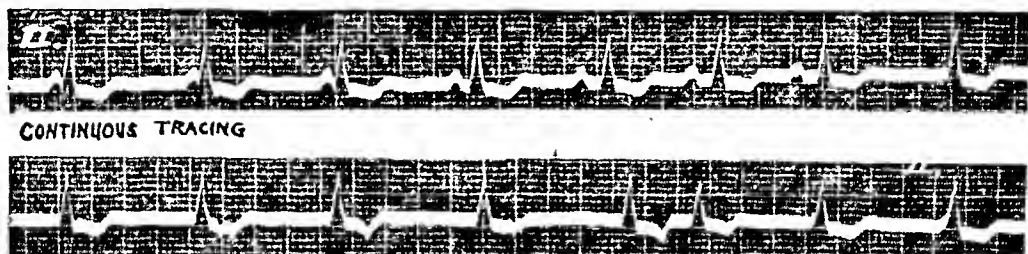


FIG. 8. *Case 7.* Malignant hypertension, hypertensive heart disease, congestive heart failure and pre-renal azotemia. Digitoxin 0.4 milligram daily for two or three months with intermittent gastrointestinal symptoms. Poor response to diuretics.

On second hospital day electrocardiograms showed interference and dissociation with abnormal form of ventricular complex ( $T_1$  inverted,  $ST_1$  and  $2$  depressed,  $T_2$  and  $3$  biphasic). Ventricular rate 76. Digitoxin discontinued.

Tracing reproduced obtained on fifth hospital day. Interference and dissociation. Note breaking up of regular rhythm by the fifth, sixth and seventh auricular beats which are conducted and cause ventricles to contract earlier. Retrograde conduction begins at tenth ventricular beat. Third beat from end shows reciprocal rhythm and aberration. Ventricular rate 80. Daily doses of digitoxin 0.1 mg. started two days later. Normal sinus rhythm recorded on twelfth hospital day.

Digitalis leaf 0.1 gm. daily started, well tolerated and followed by good diuresis.

months before admission he had been troubled with weakness, anorexia, nausea, and vomiting but this had cleared only to recur about six weeks before admission. Because of the persistence of these symptoms and a poor response to diuretic medication he was admitted to the Peter Bent Brigham on March 24, 1947.

On admission the cardiac rhythm was grossly irregular and the rate about 100 beats to the minute. Two observers noted marked variations in the intensity of the first sound at the apex.

Electrocardiograms on March 25, 1947 showed interference and dissociation, abnormal form of ventricular complex with inverted  $T_1$ , depressed  $ST_1$  and  $2$  and biphasic  $T_2$  and  $3$  and were interpreted as characteristic of left ventricular hypertrophy and very suggestive of digitalis toxicity. Digitoxin was discontinued. Tracings taken two days later showed auriculo-ventricular dissociation and sinus arrhythmia. The ventricular rate was 73 beats to the minute. On March 28, 1947 (figure 8) interference and dissociation were again present. The third complex from the end of the strip (Lead II) shows a reëntrant beat with aberrant ventricular conduction. During the next few days the electrocardiogram alternated between periods of interference and

dissociation and apparent normal conduction but eventually settled down to a persistent normal sinus rhythm.

On withholding digitoxin the anorexia, nausea, and vomiting subsided promptly and the patient now responded nicely to diuretic therapy losing seven pounds during his two week hospital stay. He was started on digitoxin 0.1 milligram daily on March 30 and then shifted to digitalis leaf 0.1 gram daily on April 4.

## DISCUSSION

The toxic rhythms described are not peculiar to digitoxin. They have been reported<sup>5-26</sup> in patients receiving the leaf of *Digitalis purpurea* and *lanata* and are probably due to one or more of the various bodies contained in the leaf, one of which, indeed, is digitoxin. A review of the general subject of digitalis therapy would be untimely. The interested reader is referred to the recent comprehensive survey of Freedberg and Zoll<sup>27</sup> which deals with digitalis in general and digitoxin in particular.

Five instances of toxicity of the type under discussion among 534 patients receiving digitalis leaf (0.9 per cent) compared with seven instances among 338 patients receiving digitoxin (2.0 per cent) at first sight suggests that the latter preparation is more prone to induce these toxic abnormal rhythms than the former. However, when these figures are subjected to statistical analysis by comparing the standard deviation of the difference (0.86 per cent) with the actual difference (1.1 per cent), that difference is not found to be significant. Hence it cannot be stated as a positive fact that digitoxin has a greater tendency than digitalis leaf to produce toxic reactions. This conclusion holds true whether there are considered to have been five or two toxic reactors among those receiving digitalis leaf.

The clinical impression remains, however, that with digitoxin these rapid rhythms may develop more insidiously than with the leaf. Cases 3 and 7 were the only ones in this series in which nausea, vomiting, or diarrhea was associated with the development of toxic rhythms. In the remaining five the abnormal rhythm itself constituted the first and only evidence of toxicity. The nausea and vomiting caused by digitalis leaf are regarded as due to its local irritant effect upon the gastric mucosa or to a central reflex effect whose mechanism is still disputed. It is held that digitoxin by virtue of the relatively small effective dosage and its virtually complete absorption has very little if any irritant effect upon the gastric mucosa and hence very little tendency to produce nausea and vomiting through a local gastric effect.<sup>1, 2</sup>

## THE RELATION OF DOSAGE TO TOXICITY

In this group of seven patients developing toxic rhythms, three had received digitoxin in amounts generally considered not to be excessive, while three had received clearly excessive dosage. In the patient (Case 6) who had received maintenance dosage of 0.2 milligram daily for months this amount may have been excessive but this would not explain why the evidences of toxicity had not developed sooner. One patient (Case 1) who

showed toxicity on small doses had received substantially larger doses of the drug at the time of a previous hospitalization without untoward effect. It seems then that toxicity is not synonymous with excessive dosage and that other factors must be involved. This experience is not new. Whereas most of the cases reported by Reid,<sup>9</sup> Luten<sup>10, 11</sup> and Marvin<sup>15</sup> followed excessive doses of digitalis, the majority of investigators<sup>5, 18, 6, 12, 13, 14, 16, 19</sup> were unable to explain the disorders on that basis and attributed them to some cardiac factor such as damaged musculature,<sup>5</sup> a changed state of the heart muscle,<sup>19</sup> an altered state of cardiac nutrition,<sup>12</sup> or to severe heart disease with congestive or anginal failure.<sup>13</sup> Vaughan considered digitalis an "exciting" factor and damaged heart muscle a "predisposing" factor. Although all of Marvin's<sup>15</sup> cases seemed to follow excessive dosage he admitted that other factors than the total amount of the drug, such as congestive heart failure or cardiac enlargement, may be responsible for the onset of these disturbances. Indeed, one might add, it is this very vulnerability of the heart to digitalis in coronary artery disease and coronary thrombosis, that, among other considerations, has militated against its use in those conditions.

It seems unlikely that this problem will be solved until some practical chemical method is available of determining the blood level of digitalis bodies. That this problem may be explained by variation in blood levels secondary to varying renal excretion of the drug is not substantiated by the present experience. The patient in severe uremia (Case 4) happened also to receive excessive doses of digitoxin. Three patients had no evidence of renal impairment and three were in mild azotemia.

More knowledge about the effect of digitalis or digitoxin on the healthy heart might clarify the subject. Our present information is fragmentary and inconclusive. The literature on this point, mostly French, describes, in individuals taking large doses accidentally or with suicidal intent, cardiac slowing from sinus bradycardia, partial auriculo-ventricular heart block, premature ventricular beats,<sup>20, 30, 31, 32, 33</sup> sinus tachycardia (rate 100),<sup>31</sup> or paroxysmal auricular tachycardia<sup>29</sup> but no disturbances of the type described above. However, because the latter are more likely to be associated with a fatal outcome and hence more easily missed, the failure to record them does not rule out their occurrence.

#### THE FAMILY RELATIONSHIP OF THE TOXIC TACHYCARDIAS

In this report the grouping together of these various arrhythmias is deliberate. Idioventricular rhythms, auriculo-ventricular dissociations and ventricular tachycardia can be regarded essentially as different degrees of the same sort of process and varying expressions of the increased irritability of the ventricles. This is well illustrated in Case 1 in which an idioventricular rhythm was recorded on the same day as bidirectional and unidirectional ventricular tachycardia. In this case an identical idioventricular rhythm was again recorded persistently on the following day during the subsidence of



digitoxin effect. It is reasonable to assume conversely that in the development of the more "advanced" toxic rhythms the heart had passed in reverse order through a similar stage of idioventricular rhythm.

### THE PREVENTION AND CLINICAL RECOGNITION OF TOXICITY

Although these abnormal rhythms may be abrupt and unpredictable in their onset they are usually foreshadowed by a rising ventricular rate. It is the duty of the attending physician to detect and evaluate such an increase in heart rate. This may be due to a progression of the underlying disease process or it may be an early indication of imminent digitalis poisoning. In Case 4 the fundamentally serious nature of the patient's illness makes it extremely doubtful that a fatal outcome would thus have been avoided; however, recognition of the rising ventricular rate might conceivably have prevented the development of this patient's terminal tachycardia.

In the absence of a practical chemical test to determine the blood level of digitalis bodies there will almost inevitably be some cases in which the physician is unable to decide whether the rising heart rate is due to a progression of the patient's disease or to digitalis poisoning. After marshaling all available evidence he is compelled to make a gamble one way or the other. The development of abnormal toxic rhythms under such circumstances (e.g. Case 5) can hardly be held to constitute an indictment of digitoxin therapy.

Another clue to the presence of such disturbances is the detection of a sudden change from a totally irregular to a regular rhythm. Although it is possible for the cardiac rhythm to revert from auricular fibrillation to a normal sinus mechanism under digitoxin therapy, it must be remembered that fundamentally digitalis bodies favor the perpetuation rather than the termination of this arrhythmia. All patients showing sudden regularization should therefore be suspected of having developed an idioventricular rhythm with complete auriculo-ventricular heart block or auriculo-ventricular dissociation. This can generally be settled only with the aid of the electrocardiogram.

Digitalis can cause the auricles and ventricles to beat independently of each other by either of two mechanisms. It can so depress auriculo-ventricular conduction that complete heart block is produced with a slower ventricular than auricular rate but generally with a more rapid ventricular rate than occurs in complete block due to most other causes. Or it can so augment the irritability of the ventricles, in the presence of normal auriculo-ventricular conduction, that the ventricles "run ahead" of the auricles. In this case (auriculo-ventricular dissociation) the ventricles beat more rapidly than the auricles. The latter mechanism is illustrated in Case 7, the former in Case 3 in which an underlying complete auriculo-ventricular block was uncovered on reversion of the heart from auricular fibrillation to normal sinus rhythm.



These observations cannot be construed as a deprecation of digitoxin therapy. They serve, rather, to sound a note of greater caution in its use. The freedom from local toxic effects and the more uniform potency of the glycoside have by and large proved a boon to patient and physician alike. But desirable as it is, their absence, in effect, deprives the attending physician of valuable warning symptoms demanding withholding of the drug. It behooves him therefore, in using digitoxin, to be even more on the alert to the insidious development of other evidences of intoxication than with digitalis leaf.

### SUMMARY

The percentile incidence of toxic rapid rhythms was greater in a group of general hospital patients receiving digitoxin than in those receiving digitalis leaf, but the difference was not statistically significant. Seven cases of digitalis poisoning among 338 patients receiving digitoxin comprised three instances of paroxysmal ventricular tachycardia, three of idio-ventricular rhythm, and one of interference and dissociation. In three cases the dosage of digitoxin was, and in three it was not, excessive. In the seventh it may have been excessive. Due to the freedom from local toxic effects with digitoxin, these toxic rhythms may be more insidious in their onset than with digitalis leaf. A rising ventricular rate or the sudden regularization of a totally irregular rhythm may serve as clues to the imminence in the one case, or the inception in the other, of these abnormal disturbances of rhythm.

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# THE HEART IN THE TERMINAL STATE: EFFECT OF INTRACARDIAC EPINEPHRINE\*

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As a consequence of recent animal experiments demonstrating the possibilities of revival of organisms, much interest has been aroused regarding the mode of death of the human heart particularly in regard to its functional deterioration. In addition, a study of the dramatic effect of intracardiac therapy on the terminal heart in patients dying from various diseases has been considered by us as a field of paramount importance particularly since we have had occasion to witness recently several instances of precipitous, unexpected, and unexplained death.

Objective studies of the effect of death on the heart must depend in great part on the use of electrocardiography, which in addition to increasing profoundly our knowledge of the heart in health and disease has aided greatly in the investigation of the heart in its clinical and subsequent biologic death. The electrocardiogram has demonstrated repeatedly that clinical death characterized by the disappearance of heart sounds and cessation of respiration is followed in many cases for a variable and at times a prolonged period by cardiac activity. Certain measures designed to revive a dying myocardium may some day make possible resumption of circulation adequate for continuation of life for a time. This possibility makes desirable an analysis of any knowledge which exists at present or which may be obtained in this investigation, concerning the sequence of events immediately preceding the total cessation of cardiac activity.

## REVIEW OF LITERATURE

The original work of Rohmer<sup>1</sup> in 1911 represents the first reference to electrocardiograms taken during the last moments of human life. Rohmer pointed out that in three fatal cases of diphtheria, terminally the auricles and ventricles beat independently and that the QRS complex assumed an abnormal form. Robinson<sup>2</sup> in 1912 published a study of electrocardiographic observations made in seven patients dying of acute infectious diseases. In four cases ventricular activity outlasted the auricular activity while in two the reverse was true. Cardiac activity was revealed by the electrocardiograph, six to 35 minutes after all the usual clinical signs of death had appeared. Marked slowing of the rate of cardiac activity always occurred and there was usually distinct delay in the conduction time between auricles and ventricles. Ventricular fibrillation occurred in only two cases and in one

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of these, a sinus rhythm was transiently reestablished. Eventual fusion of the R- and T-waves was a constant occurrence. Auricular fibrillation was not encountered.

In 1915 Halsey<sup>3</sup> described an almost complete electrocardiographic record of the heart during the last moments of a patient dying from bronchopneumonia. Slowing of the heart rate was marked, then increasing auriculo-ventricular conduction occurred with appearance of abnormal QRS complexes and ventricular fibrillation appeared shortly before death. Dieuaide and Davidson<sup>4</sup> in 1921 reported records of patients dying of intrinsic heart disease in two of which the electrocardiograms were taken during death resulting from arteriosclerotic and hypertensive heart disease. Slowing of the cardiac rate occurred along with lengthening of the P-R and QRS intervals, appearance of auriculoventricular nodal rhythm, complete dissociation of auricles and ventricles and various arrhythmias including auricular and ventricular extrasystoles, ventricular tachycardia and auricular and ventricular fibrillation. Schellong<sup>5</sup> in 1923 found similar phenomena to occur in electrocardiograms based on studies in 20 dying patients. In addition he pointed out that T-waves in dying hearts were noted to increase in size and become positive even when previously negative. Willius<sup>6</sup> in 1924 presented a study on changes in the mechanism of the human heart preceding and during death. He found that in each instance of six patients, auricular activity ceased before that of the ventricles. Nodal rhythm occurred frequently as did complete heart block. Ventricular fibrillation appeared in four cases and was the terminal mechanism in three. Periods of cardiac standstill occurred lasting from 9.4 to 11.4 seconds. He concluded that the terminal changes in the mechanism of the human heart probably resulted from vagal influences and from alterations in the inherent activity of the heart due to the influences accompanying death.

An interesting study on the dying human heart by Kahn and Goldstein<sup>7</sup> in 1924 stressed the initial failure of the sinus node with the assumption of control by the auriculo-ventricular node as the most significant phenomenon in terminal heart activity. They pointed out that the sinus node first shows irritability and depression in various sequences and in varying degree and if such disturbances could be controlled before cessation of sinus function, recovery might occur. Martini and Sckell<sup>8</sup> in 1928 studied 17 patients and found similar terminal phenomena to those which had been previously published. Fatigue of the sinoauricular node resulted in an auriculoventricular nodal rhythm. The R- and T-waves tended to merge. The longest interval in which electrical manifestations persisted after clinical death was nine and a half minutes. Turner<sup>9</sup> in 1931 reviewed electrocardiographic observations on the death of the human heart in 65 cases contained in the literature and presented a detailed study of five cases of his own. He found as did the others that conspicuous slowing of the heart rate was the most constant change in the cardiac mechanism immediately preceding death. Also frequently encountered was the appearance of an auriculoventricular nodal

rhythm or an idioventricular rhythm. The age of the patient or the presence or absence of cardiac disease did not condition the manner in which the heart died. Significant changes appeared in the electrocardiogram often only a few minutes before clinical death. Hanson, Purks, and Anderson<sup>10</sup> a few years later (1933) reported 25 cases in which electrocardiograms were taken during death. They encountered 10 instances of ventricular fibrillation and this rhythm represented the terminal event in cessation of cardiac activity in nine of the 25 cases. The sequence of events otherwise was similar to those of previous reports. The last five cases of their series after standstill of both the auricles and ventricles had occurred, were treated with intracardiac injection of adrenalin in the third left intercostal space close to the sternum and in four of them a transient return of monophasic complexes appeared in the electrocardiogram only to end in terminal ventricular fibrillation.

Sigler and co-workers<sup>11</sup> in 1937 reported electrocardiographic studies on 20 cases before, during, and after clinical death. In some instances electrocardiographic activity was noted as long as one hour after clinical death. The main changes noted included initial sinus acceleration followed by sinus bradycardia, sinoauricular standstill and then nodal rhythm, ventricular extrasystoles, increasing and variable auriculoventricular block, intraventricular block, changes in ventricular complexes, variable cessation of auricular activity and ventricular fibrillation. Levin<sup>12</sup> in 1939 published a good description of two terminal electrocardiograms and concluded that death of the heart occurred in three phases, first sinus bradycardia due to apnea, then either a nodal or ventricular rhythm and finally a slow rhythm with huge T-waves and gradual cessation. In the foreign literature Mayer, Pataro and Lepera<sup>13</sup> in 1941 reviewed the literature and discussed a patient in whom an injection of intracardiac adrenalin was given at clinical death and resulted in transient changes from nodal rhythm to sinus rhythm for the 33 minutes in which the electrocardiogram was followed.

### RESUSCITATION OF THE HEART

Hyman<sup>14</sup> in 1930 published an excellent report on the resuscitation of the stopped heart by intracardiac therapy. He pointed out that the increasing use of epinephrine for intracardiac injection in emergency conditions arising in the operating room as well as elsewhere has been attended by such inconstant results that physicians are at a loss in evaluating the efficacy of the procedure. As a result he attempted a systematic study of this problem. In a review of the literature he found that the intracardiac method of resuscitation had been employed in a total of about 250 cases up to 1930 and that a favorable outcome appeared to be experienced in about 25 per cent. Levine and Matton<sup>15</sup> in 1926 reported a case of Adams-Stokes syndrome wherein ventricular fibrillation occurred for a period of 3.5 minutes and was followed by ventricular standstill for 79 seconds in which intracardiac injection of

adrenalin returned the mechanism to a normal rhythm enabling the patient to leave the hospital.

Intracardiac injection has been considered as including either injection into the wall of the heart or the chambers of the heart particularly that of the ventricles. Any other intravenous route of medication would obviously be ineffective since in such instances circulation is at a standstill. Further consideration also led Hyman to believe that injection into the chambers of the heart would be just as ineffective since with cardiac cessation there is no more circulation within the cardiac chambers than in the arterial or venous circulation. He recommended injection of the drug in the wall of the heart based on experience in the experimental laboratory in which the isolated mammalian heart may be stimulated to contraction following a period of standstill when epinephrine and other substances are injected into the myocardium. Occasional favorable results have also resulted clinically from the use by the intracardiac injection of such drugs as digitalis, camphor, ether, strophanthin, metrazol, coramin, strychnine, hypertonic salt solution, caffeine and dextrose. The large number of substances used for intracardiac therapy suggests that the effect of these drugs may be somewhat non-specific in their action.

Resuscitation of the heart by direct or indirect manipulation has been practiced for many years by numerous surgeons for cardiac arrest during surgical procedures. The attempt is made to massage the heart by direct pressure on the diaphragm or thorax or by squeezing, pinching or any mechanical means of irritating the heart to contract again. Various mechanical devices for stimulating the heart have been devised. However, in a patient dying from a non-surgical condition there is no opportunity mechanically to stimulate the heart. Obviously a direct and rapid route of cardiac stimulation is indicated in dying patients. Hyman concluded that the intracardiac injection procedure is satisfactory and its effectiveness is due primarily to the effect of the puncture wound on the myocardium rather than to the chemical substance injected. Anoxemia makes the myocardium irritable and any mechanical stimulation such as massage or injecting a needle may produce a wound which becomes a focus of increased irritability from which a stimulus may develop and produce initially extrasystoles and subsequent sinus rhythm and recovery, although with more prolonged anoxemia and permanent ventricular muscle changes abnormal rhythm such as ventricular fibrillation may result with no opportunity of resuscitation. For this latter reason Hyman recommended intracardiac puncture be made into the right auricle and stressed that the auricles are more responsive to mechanical stimulation than the ventricles.

For clinical purposes, the patients favorable for resuscitation are those in whom the heart is relatively normal and where there is no serious generalized disease. Especially favorable situations are those instances of cardiac arrest on the operating table, during anesthesia, shock, accidents, sudden collapse, so-called "status lymphaticus," and asphyxia neonatorum. An-

other important consideration is the period which has elapsed between the time of arrest of the circulation and the attempt at resuscitation. Particular study has been made of the exact duration of time during which the circulation can be arrested before nerve cells die and vital centers cannot be revived. However, there has been no uniformity of opinion in this regard. In human beings, clinical and pathologic studies are lacking on the effects of anoxia and the resultant neuronal damage due to cardiac arrest. Although successful cardiac massage has been performed by numerous surgeons for cardiac arrest during surgical procedures, permanent success without cerebral damage has been limited to cases in which the critical time limit of five minutes has not been exceeded. Three British investigators<sup>16</sup> have recently reported a case of prolonged cardiac arrest occurring during surgical intervention. The fatal duration of cardiac arrest was 10 to 11 minutes. Transdiaphragmatic cardiac massage was successful in reestablishing the cardiac beat. During the survival period of 26 days the patient's condition resembled modified decerebrate rigidity and she died of intercurrent infection. Obviously therefore attempts at resuscitation must be performed not only skillfully but also speedily before the extreme sensitivity of the brain to anoxemia, ischemia, and anemia has resulted in irreparable and irreversible damage.

### METHOD OF STUDY

This paper presents electrocardiographic changes occurring before, at the time of, and after clinical death in a series of 34 cases. In many instances tracings were started several hours before expected death and continued from time to time until biologic death occurred. In addition many of the patients had electrocardiograms for days, weeks, or even months prior to the fatality. In our series an attempt was made to obtain tracings in the standard and CF4 leads during the early events preceding death but shortly before and after death events were recorded only in Lead II. In most instances, complete data were obtained including the chronologic occurrences in reference to the electrocardiograms of clinical death, cessation of heart sounds and respiration, and the time of appearance of the very last complex in the heart tracings. Factors such as age, sex, primary and immediate cause of death, cardiac status, clinical findings, such as terminal temperature, blood pressure, presence of shock or cardiac failure, presence or absence of anemia, and findings at autopsy were all studied and attempts made at correlation with the terminal findings in mind.

In addition to the study on the nature and mode of cessation of cardiac activity, equal consideration was given to the effect of intracardiac injection of 1 to 2 c.c. of 1-10,000 solution of epinephrine both directly into the myocardium and into the cardiac chambers usually immediately after all the deflections in the electrocardiogram had ceased. This part of the study presented an opportunity to study the physiologic ramifications of the intra-

cardiac injection method of resuscitating the dying heart. The intracardiac injection was performed by using a 21 gauge 4 inch length needle and inserting it slowly into the fourth left intercostal space and pulling on the plunger of the syringe until blood was obtained and then injecting the epinephrine. The myocardial infiltration was performed in essentially the same manner except that when the point was reached at which the blood was obtained, the needle was withdrawn extremely slowly until the exact point was reached when blood could just no longer be obtained and then the epinephrine was injected presumably into the myocardium.

## RESULTS

This series included 23 males and 11 females. The causes of death varied and included among other conditions, 11 patients with some form of heart disease and 11 with carcinomatosis. The duration of the primary disease varied from four weeks to 12 years. The ages varied from 18 to 79 years with an average of 57.4 years. Twenty-four of the 34 patients had postmortem examinations. Terminally most of the patients were mentally in a comatose or markedly obtunded condition. With the exception of one patient who had an exploratory thoracotomy, none of the deaths were post-operative. Various medications were given in the terminal period but these appeared to have no specific influence on the course of the patients in the final stages. Terminal temperatures varied from subnormal to very high ranges. Seven of the 34 patients had for comparison one or more electrocardiograms previous to their terminal illness. The terminal electrocardiograms were begun over a range of 1 to 35 minutes (average of 9.2 minutes) before cessation of respiration, and continued for a period of 50 seconds to 22 minutes (average of 5.9 minutes) after respiration had ceased. In 11 of the 34 patients in whom sufficient attention could be spared it was noted that the terminal complex in the electrocardiogram occurred 3.3 to 17 minutes (average of 5 minutes) after the heart beat became imperceptible.

## SUMMARY OF ELECTROCARDIOGRAPHIC CHANGES

Table 1 contains a summary of the terminal electrocardiographic changes. In the records taken early in the terminal period 30 cases presented a sinus rhythm and four auricular fibrillation. One case had left bundle branch block. A great variety of rapidly shifting arrhythmias and changes in rate occurred. Initial sinus acceleration of the cardiac mechanism was frequent, but slowing of the rate prior to death was always encountered with the exception of two patients in whom an abrupt change of the mechanism to ventricular tachycardia occurred. With progressive sinus slowing and associated sinoauricular node depression, periods of sinoauricular block appeared in three cases. Sinoauricular standstill occurred in five patients. During life, when sinus node depression and inhibition occur, the center of next greatest inherent rhythmicity, which is usually the auriculoventricular



TABLE I  
Summary of Terminal Electrocardiographic Changes

Case No.	Age	Sex	Diagnosis	Sequence of Events in Electrocardiogram
1	62	M	Portal cirrhosis; bleeding esophageal varices	Progressive prolongation of P-R interval; 3 to 1 A-V block; cessation of ventricles; cessation of auricles.
2	55	M	Hypertensive heart disease; acute posterior myocardial infarction	Changes of acute posterior myocardial infarction; ventricular extrasystoles; complete A-V block; ventricular extrasystoles from 3 foci.
3	53	F	Portal cirrhosis	Abnormal form of ventricular complex with low voltage, sinus tachycardia, auricular extrasystoles; sinoauricular block; nodal rhythm, 45 per minute; complete A-V block, 25 per minute; markedly abnormal ventricular complex; cessation of ventricle; cessation of auricle; epinephrine given, no effect.
4	52	M	Congenital heart disease; tetralogy of Fallot	S-type bundle branch block; nodal tachycardia; cessation of auricles; idioventricular rhythm, rate 48 per minute; ventricular extrasystoles.
5	72	F	Acute posterior myocardial infarction; bronchopneumonia	Changes of acute posterior myocardial infarction, auricular fibrillation, left axis deviation; auricular fibrillation, with complete block; idioventricular rhythm 38 per minute; asystole for 10 seconds; sinus rhythm.
6	79	F	Acute myocardial infarction; arteriosclerotic heart disease; auricular fibrillation	Myocardial damage of coronary type, auricular fibrillation, ventricular extrasystoles, digitalis effect; gradual slowing of ventricular beats to 25 per minute, then 12 per minute and then complete cessation.
7	18	F	Rheumatic heart disease with aortic stenosis and insufficiency and mitral stenosis and insufficiency	Auricular fibrillation with ventricular extrasystoles; auricular flutter with 5 to 1 block, cessation of ventricle; regular auricular beats with progressive slowing.
8	55	M	Squamous cell carcinoma of larynx; bronchopneumonia	Sinus rhythm; sinus bradycardia; nodal tachycardia; ventricular tachycardia; ventricular flutter, ventricular fibrillation.
9	56	M	Carcinoma of stomach with metastases	Sinus rhythm; sinus bradycardia; runs of nodal extrasystoles; nodal rhythm, markedly abnormal ventricular complexes with QRS duration of .24, depressed ST complexes and low voltage.
10	69	M	Carcinomatosis; bronchopneumonia	Abnormal form of ventricular complex, low voltage; sinus tachycardia; sinus bradycardia; prolonged P-R interval; partial heart block; cessation of ventricle; cessation of auricle; epinephrine given, no effect.
11	40	F	Myelogenous leukemia	Abnormal form of ventricular complex, low voltage, sinus bradycardia, sinoauricular block; ventricular extrasystoles.
12	68	M	Arteriosclerotic heart disease	Myocardial damage of coronary type; sinus tachycardia; sinus bradycardia; partial heart block, nodal rhythm, idioventricular rhythm.

TABLE I—*Continued*

Case No.	Age	Sex	Diagnosis	Sequence of Events in Electrocardiogram
13	65	M	Arteriosclerotic heart disease; acute posterior infarction	Changes of an acute posterior myocardial infarction; sinus tachycardia; sinus bradycardia; ventricular extrasystoles from 2 foci; asystole for 53 seconds; ventricular fibrillation; idioventricular rhythm with progressive slowing.
14	67	M	Arteriosclerosis; diverticulosis of colon; acute anterior myocardial infarction	Changes of an acute anterior myocardial infarction; sinus bradycardia; complete A-V block; auricular standstill; markedly abnormal ventricular complex with extreme slurring, duration of .24, elevation of ST segments; epinephrine given, no effect.
15	67	M	Arteriosclerotic heart disease; prostatectomy 4 days before death	Abnormal form of ventricular complex, sinus rhythm; ventricular tachycardia; asystole for 33 seconds; cessation of auricle; idioventricular rhythm at 30 per minute with progressive slowing.
16	38	F	Myelogenous leukemia	S-type bundle branch block, sinus rhythm; prolonged P-R interval; partial heart block; varying periods of auricular standstill; complete heart block.
17	58	M	Bronchiogenic carcinoma; exploratory thoracotomy	Abnormal form of ventricular complex; sinus tachycardia; sinus bradycardia; nodal rhythm; complete A-V block; auricular standstill; idioventricular rhythm becoming irregular; very abnormal ventricular complexes with depressed ST complexes and QRS duration of .30; epinephrine given with production of a short run of regular ventricular beats.
18	28	M	Carcinoma of lung	Sinus rhythm, sinus tachycardia; sinus bradycardia, partial heart block changing from 2 to 1 to 4 to 1; cessation of ventricle, cessation of auricle, epinephrine given, no effect.
19	66	M	Carcinoma of trachea	Myocardial damage of coronary type; sinus rhythm; auricular standstill; alternating bundle branch block; ventricular extrasystoles.
20	57	M	Reticulum cell sarcoma; bronchopneumonia	Sinus rhythm; nodal rhythm with progressive slowing; epinephrine given; mixed ventricular flutter and fibrillation for 2 minutes.
21	66	F	Carcinoma of gall-bladder	Abnormal form of ventricular complex, sinus rhythm; shifting auricular pacemaker; nodal beats; ventricular extrasystoles.
22	54	F	Leukosarcoma; lobar pneumonia	Sinus rhythm; sinus bradycardia; 2 to 1 A-V block; auricular standstill; epinephrine given; ventricular rate increased; auricular beats reappeared, sinus bradycardia; sinus pauses; irregular nodal beats.
23	49	M	Adenocarcinoma of liver	Abnormal form of ventricular complex; auricular fibrillation; ventricular fibrillation; epinephrine given, no effect.
24	75	M	Adenocarcinoma of ? origin	Sinus rhythm; nodal rhythm; idioventricular rhythm; markedly abnormal QRS complexes with duration of .32, depression of ST segments; epinephrine given; change to sinus rhythm with normal ventricular complexes; contractions continued for 36 minutes after cessation of respiration.

TABLE I—*Continued*

Case No.	Age	Sex	Diagnosis	Sequence of Events in Electrocardiogram
25	53	M	Myelogenous leukemia	Sinus rhythm; sinus bradycardia; nodal rhythm; ventricular extrasystoles; ventricular tachycardia; ventricular fibrillation; epinephrine given, no effect.
26	72	M	Severe anemia; shock	S-Type bundle branch block; low voltage; ventricular extrasystoles, cardiac standstill; epinephrine given in ventricular chamber, no effect; given in myocardium, ventricular beats obtained for 1.5 minutes; myocardial injection repeated, no effect.
27	59	F	Carcinoma of ovary with metastases to lung	Myocardial damage of coronary type; sinus rhythm; sinus bradycardia; partial heart block; idioventricular rhythm; mixed ventricular flutter and fibrillation; epinephrine in cardiac chamber; no effect; myocardial injection given, ventricular fibrillation.
28	62	F	Generalized carcinomatosis; bronchopneumonia	Myocardial damage of coronary type; sinus tachycardia; sinus bradycardia, sinoauricular block; nodal rhythm; cessation of ventricle, cessation of auricle; epinephrine given in myocardium, no effect.
29	78	M	Chronic lymphatic leukemia	Left bundle branch block, sinus rhythm; shifting auricular pacemaker; auricular extrasystoles, nodal extrasystoles; epinephrine given in cardiac chamber, no effect.
30	52	M	Adenocarcinoma of liver	Abnormal form of ventricular complex, sinus rhythm, sinus tachycardia; sinus bradycardia to 15 per minute; epinephrine given, no effect.
31	51	M	Subacute glomerulonephritis	Sinus rhythm, sinus bradycardia; nodal rhythm, complete A-V block; irregular ventricular beats, cessation of ventricle; cessation of auricle; epinephrine given, no effect.
32	61	M	Hypertensive heart disease	Abnormal form of ventricular complex; sinus rhythm, ventricular fibrillation.
33	39	F	Malignant hypertension	Abnormal form of ventricular complex, sinus rhythm; sinus bradycardia, ventricular tachycardia, asystole for 11 seconds; ventricular fibrillation; epinephrine given into right auricle, no effect.
34	56	M	Hypertension; uremia	Auricular fibrillation; complete A-V block; epinephrine given in myocardium; ventricular fibrillation; asystole for 1 minute; mixed ventricular flutter and fibrillation; ventricular fibrillation.

node, becomes the pacemaker. A similar mechanism developed in these terminal records for auriculoventricular nodal rhythm appeared in 11 and an idioventricular rhythm in seven more of the 34 cases. Ventricular extrasystoles assumed control at intervals in nine patients with multiple foci in two instances, while nodal and auricular extrasystoles appeared in five cases.

As death became very imminent, increasing auriculoventricular conduction was a fairly common finding with the development of partial heart block in five instances and complete block in eight cases. Most of the usual arrhythmias were encountered in these terminal records. Auricular fibrilla-

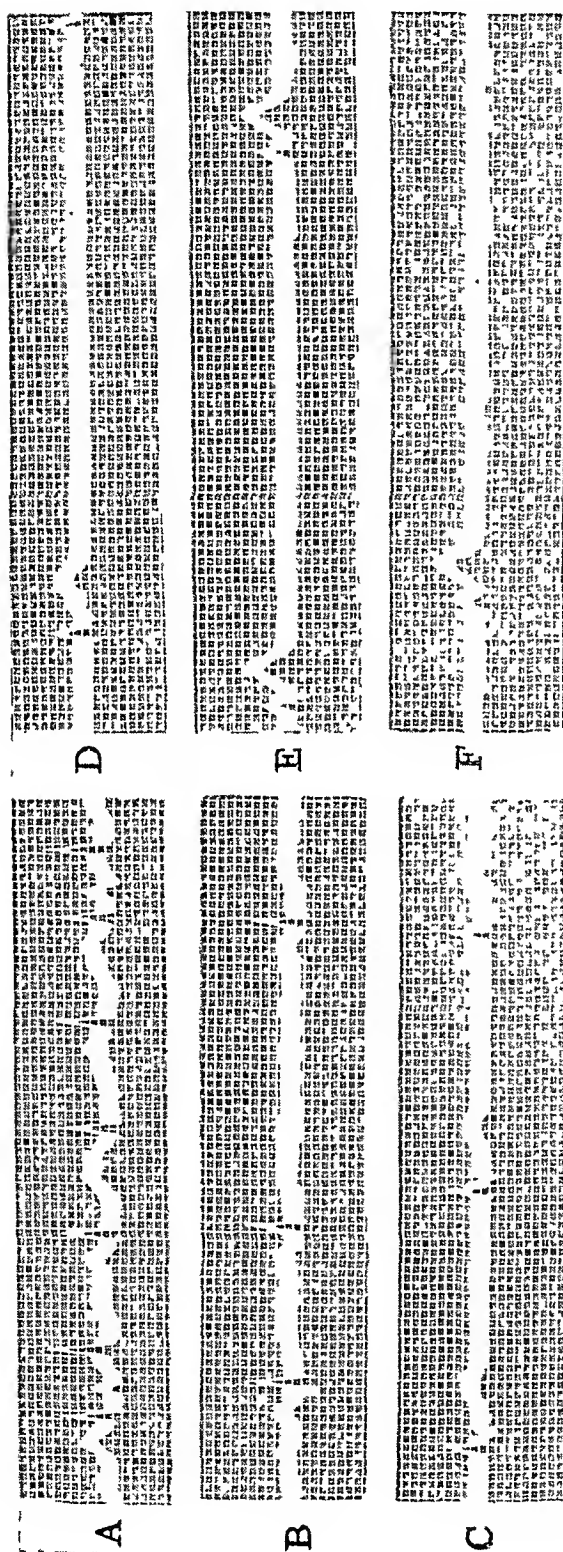


Fig. 1. Sequence of events in case 3. Lead II. A. Sinus tachycardia, auricular extrasystoles. B. Sino-auricular block. C. Nodal rhythm. D. Complete A-V block. E. Abnormal ventricular complexes. F. Initial cessation of ventricle.

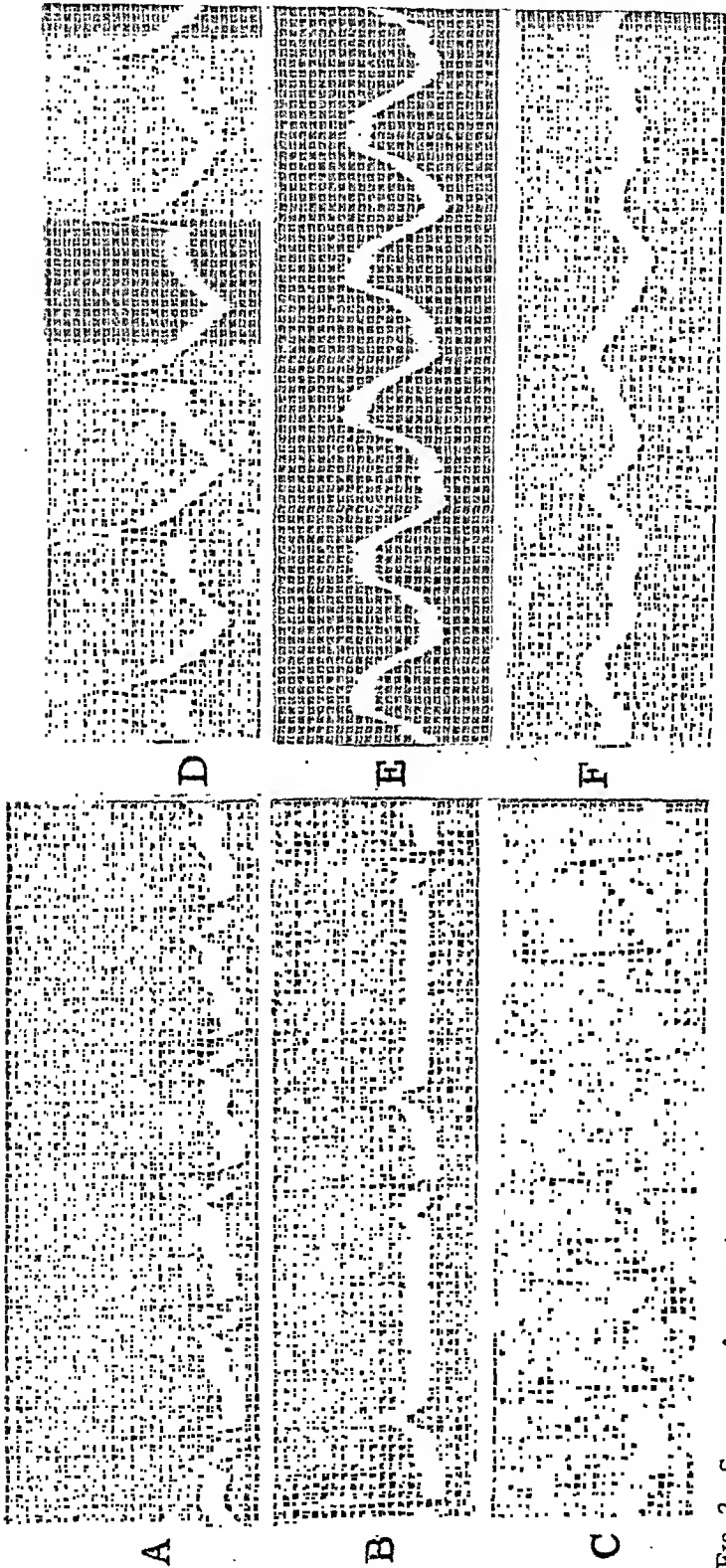


FIG. 2. Sequence of events in case 8. Lead II. A. Sinus rhythm. B. Sinus bradycardia. C. Nodal tachycardia. D. Ventricular tachycardia. E. Ventricular flutter. F. Ventricular fibrillation.

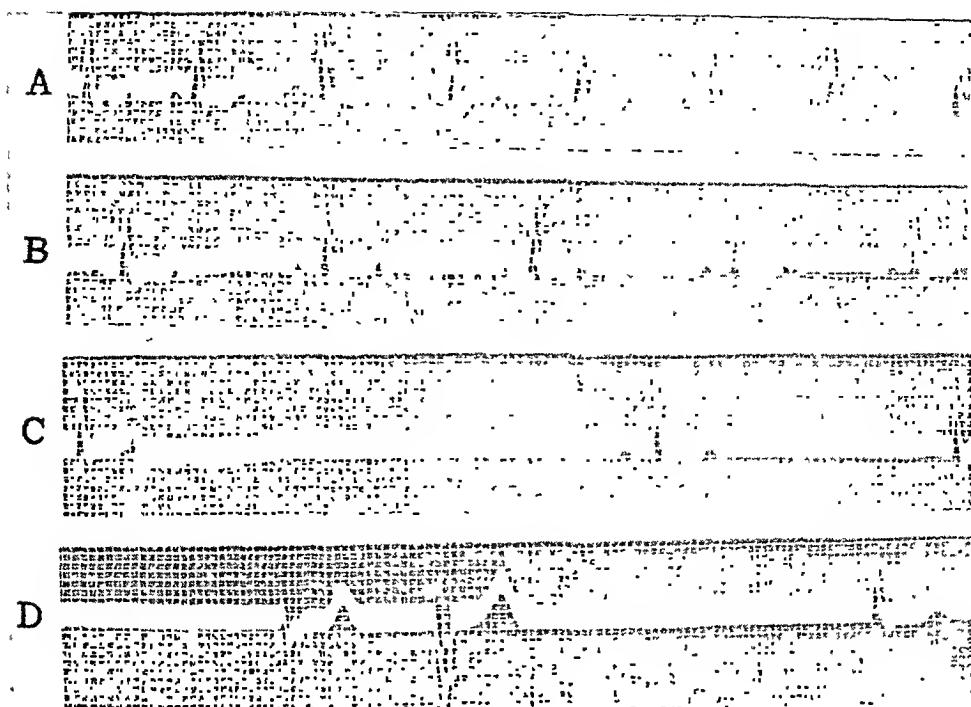


FIG. 3. Sequence of events in case 11. Lead II. A and B. Sinus rhythm. C. Sinoauricular block. D. Ventricular extrasystoles.

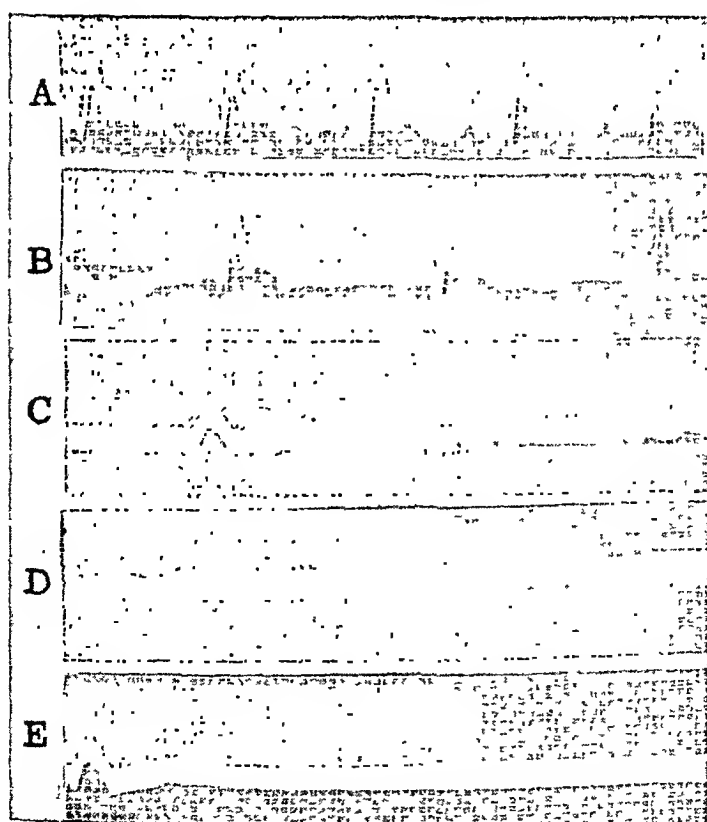


FIG. 4. Sequence of events in case 13. Lead II. A and B. Changes of acute posterior infarction with sinus rhythm. C. Ventricular extrasystoles from two foci. D. Asystole lasting 53 seconds. E. Idioventricular rhythm with progressive slowing.

tion, however, did not occur with the exception of the four patients who had had this rhythm prior to the onset of the terminal state; in one of these instances the auricular fibrillation changed to auricular flutter. Ventricular fibrillation was fairly common having been encountered in nine cases, usually as a terminal event, whereas ventricular tachycardia and ventricular flutter each occurred in four patients. The latter two ventricular rhythms appeared always in association with ventricular fibrillation with only one exception.

The final complex in the electrocardiogram after death represented ventricular activity in 27 instances and auricular activity in seven cases. Intra-

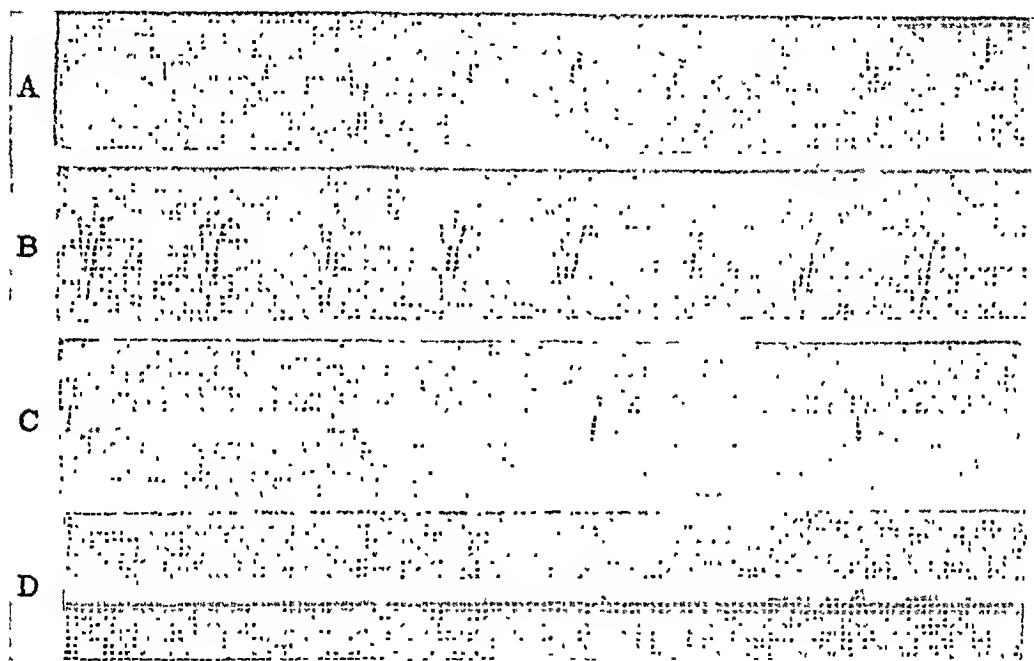


FIG. 5. Sequence of events in case 15. Lead II. A. Sinus rhythm with ventricular extrasystoles. B. Ventricular tachycardia. C and D. Idioventricular rhythm with progressive slowing.

ventricular disturbances included particularly marked prolongation of the QRS duration (maximum of .52 second) in 28 patients with associated slurring especially of the S-wave. The voltage of the QRS complex was low in 20 cases and increased in only one. Various changes occurred in the character of the RST segments including elevation, depression, rounding and lengthening. The T-waves often changed precipitously by becoming inverted, upright, abnormally high or isoelectric. Significant periods of asystole of both the auricle and ventricle occurred in six cases with the asystolic period varying from 10 to 60 seconds. Figures 1 to 11 illustrate the sequence of events and terminal occurrences in characteristic cases.

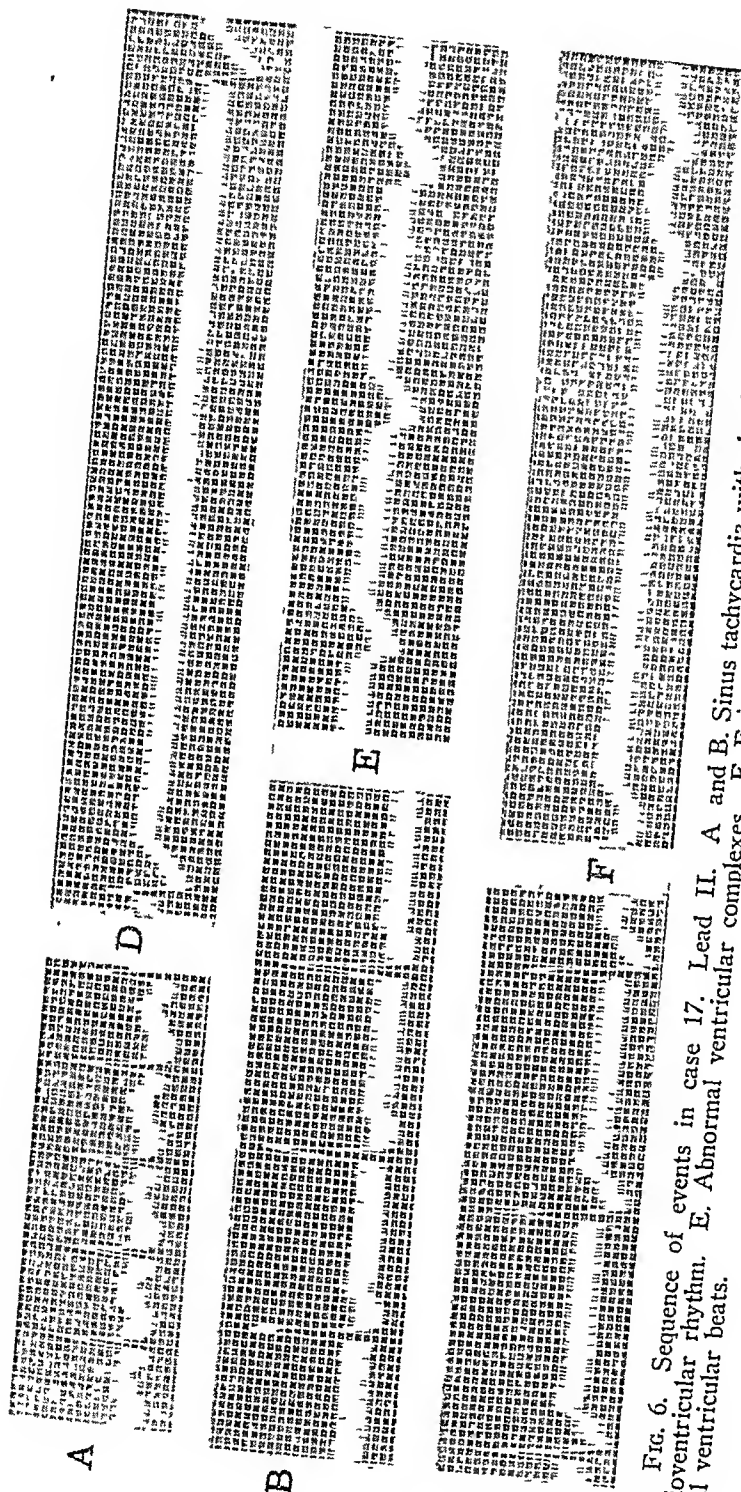


FIG. 6. Sequence of events in case 17. Lead II. A and B, Sinus tachycardia with slowing. C, Nodal rhythm. D, abnormal ventricular complexes. E, Epinephrine given with resultant short run of very abnormal ventricular beats.



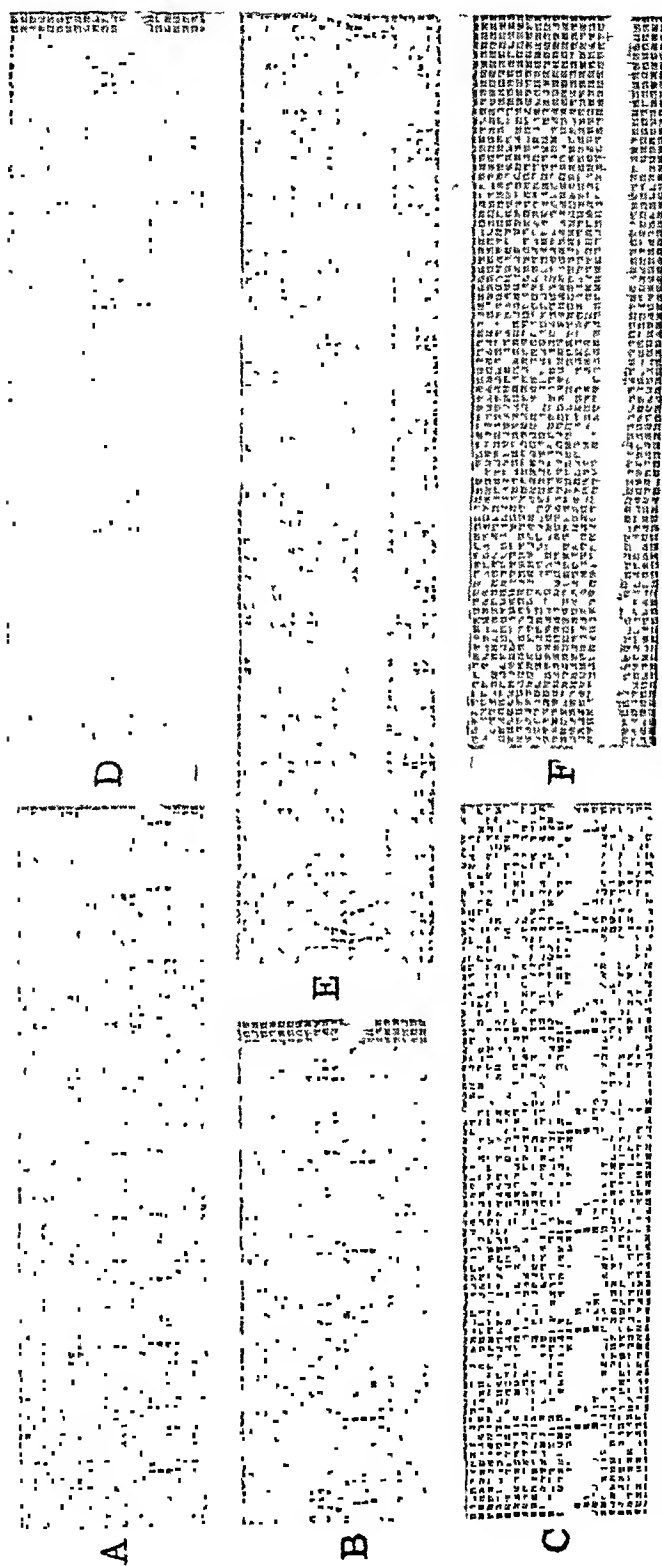


FIG. 7. Sequence of events in case 18. Lead II. A, B, C, and D. Sinus rhythm with progressive slowing. E, 3 to 1 A-V block. F. Terminal auricular beats. Epinephrine given without effect.

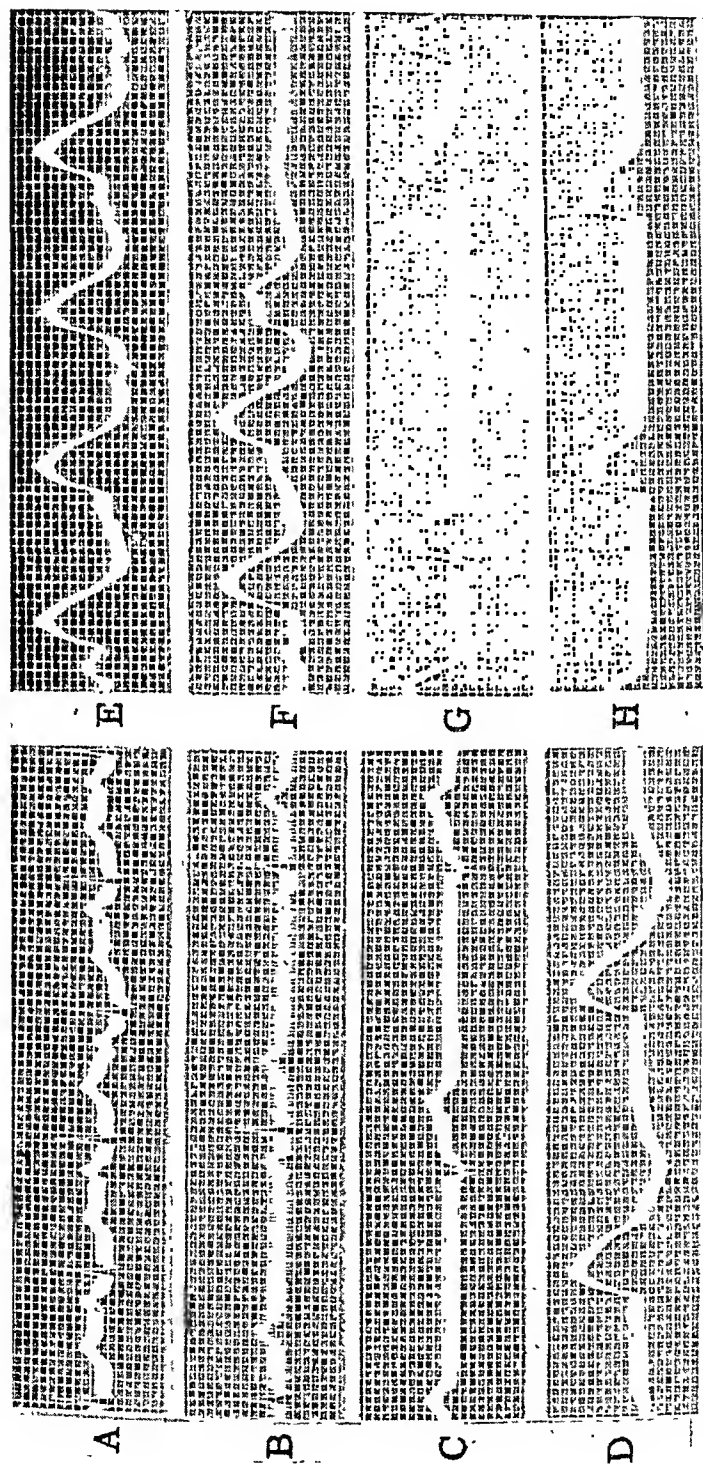


Fig. 8. Sequence of events in case 24. Lead II. A. Sinus tachycardia. B. Sinus bradycardia. C. Nodal rhythm. D. Idioventricular rhythm with very abnormal ventricular complexes. E. Epinephrine given with change to sinus rhythm. F, G, and H. Continuation of ventricular complexes for 36 minutes after cessation of respiration.

## EFFECT OF INTRACARDIAC EPINEPHRINE

The 18 cases of the series in which epinephrine was injected into the heart in the study of cardiac resuscitation are worthy of special consideration. Table 2 presents a summary of the results obtained from intracardiac epinephrine. In 10 patients the adrenalin was injected directly into the ventricular chamber and in one case it was put into the right auricle. In nine instances it was injected presumably into the ventricular myocardium. In two of the 18 cases the epinephrine was initially placed in the cardiac cham-

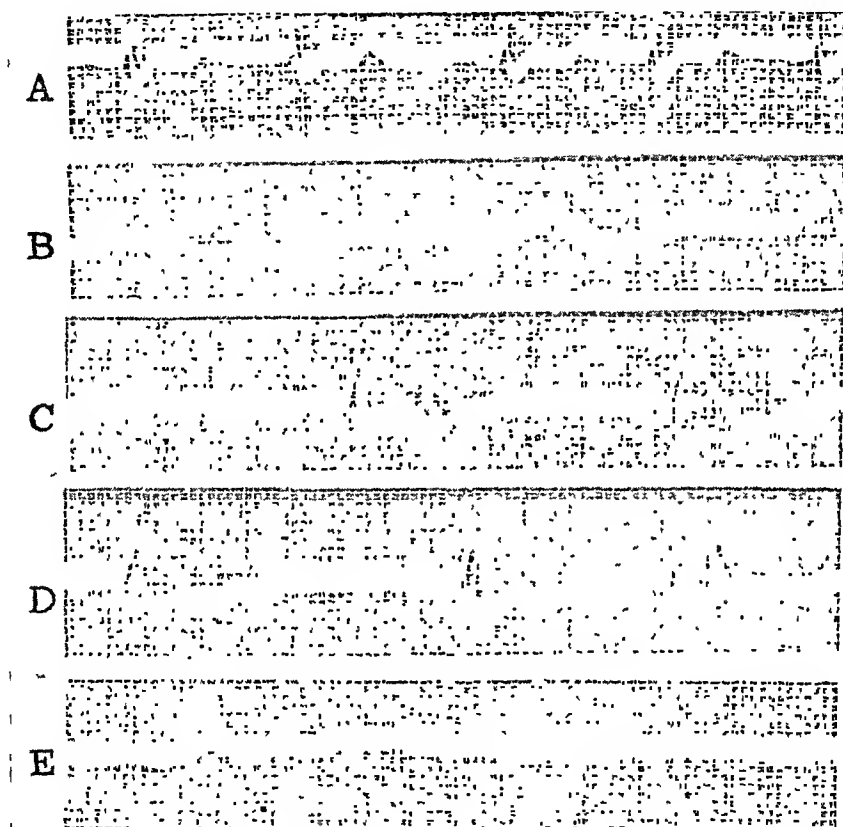


FIG. 9. Sequence of events in case 26. Lead II. A. S-type bundle branch block. Between A and B, cardiac standstill occurred and epinephrine given into cardiac chamber without effect. Epinephrine then given into myocardium, and B, C, D, and E show the resultant ventricular beats which persisted for 1.5 minutes.

ber and when no effect was noted, an additional injection was made into the myocardium with production of a few ventricular extrasystoles in one instance and ventricular flutter and fibrillation in the other. Care was exercised to notice whether the injection of the needle alone in five cases had any effect and none could be demonstrated. In the entire group of 18 patients only seven showed a response to the epinephrine injections including five of nine cases (56 per cent) submitted to myocardial infiltration with adrenalin and only two of 11 cases (18 per cent) treated by injection into the cardiac chambers. Of the total of seven patients in whom an effect was obtained,

the injection produced ventricular fibrillation in three instances and ventricular extrasystoles in two cases and restored the regular ventricular beats in the other two patients in one of whom the beats continued for 36 minutes after respiration had ceased. Figures 6 to 11 demonstrate the effects encountered with intracardiac and myocardial injections of epinephrine.

### DISCUSSION

The factors of age, sex, clinical findings, primary disease, precipitating cause of death, presence or absence of heart disease, or anemia, and findings at autopsy appeared to have no conditioning effect on the mechanism of death judging from the electrocardiographic manifestations. The findings in our

TABLE II  
Summary of Results from Intracardiac Epinephrine

Case No.	Epinephrine in Cardiac Chamber	Epinephrine in Myocardium	Result
3	Yes	—	No effect
10	—	Yes	No effect
13	Yes	—	No effect
14	Yes	—	No effect
17	Yes	—	Ventricular extrasystoles for 8 seconds
18	—	Yes	No effect
20	—	Yes	Ventricular flutter and fibrillation
22	—	Yes	Restoration of original sinus rhythm
23	Yes	—	No effect
24	Yes	—	Restoration of original sinus rhythm
25	—	Yes	No effect
26	Yes	Yes	No effect from injection into chamber. Myocardial injection produced ventricular extrasystoles for 1.5 minutes
27	Yes	Yes	No effect from injection into chamber. Myocardial injection produced ventricular fibrillation
28	—	Yes	No effect
29	Yes	—	No effect
30	Yes	—	No effect
31	Yes	—	No effect
33	(right auricle)	—	No effect
34	—	Yes	Ventricular flutter and fibrillation

series do not differ significantly from those reported by previous investigators. Although initial sinus acceleration often occurred, a conspicuous slowing of cardiac rate just before death was a most constant finding. Almost just as frequent was the occurrence of increasing auriculoventricular and intraventricular conduction times as death ensued. Ventricular fibrillation was the terminal rhythm in approximately 26 per cent of cases.

From the physiologic point of view the initial sinus acceleration is due primarily to transient sympathetic nerve irritability. Very shortly before death the vagus centers in the medulla are apparently stimulated producing in practically every terminal heart, a marked vagotonic state resulting in sinoauricular node and auriculoventricular conducting bundle depression. The fundamental factors of toxemia, asphyxia and local nutritional changes

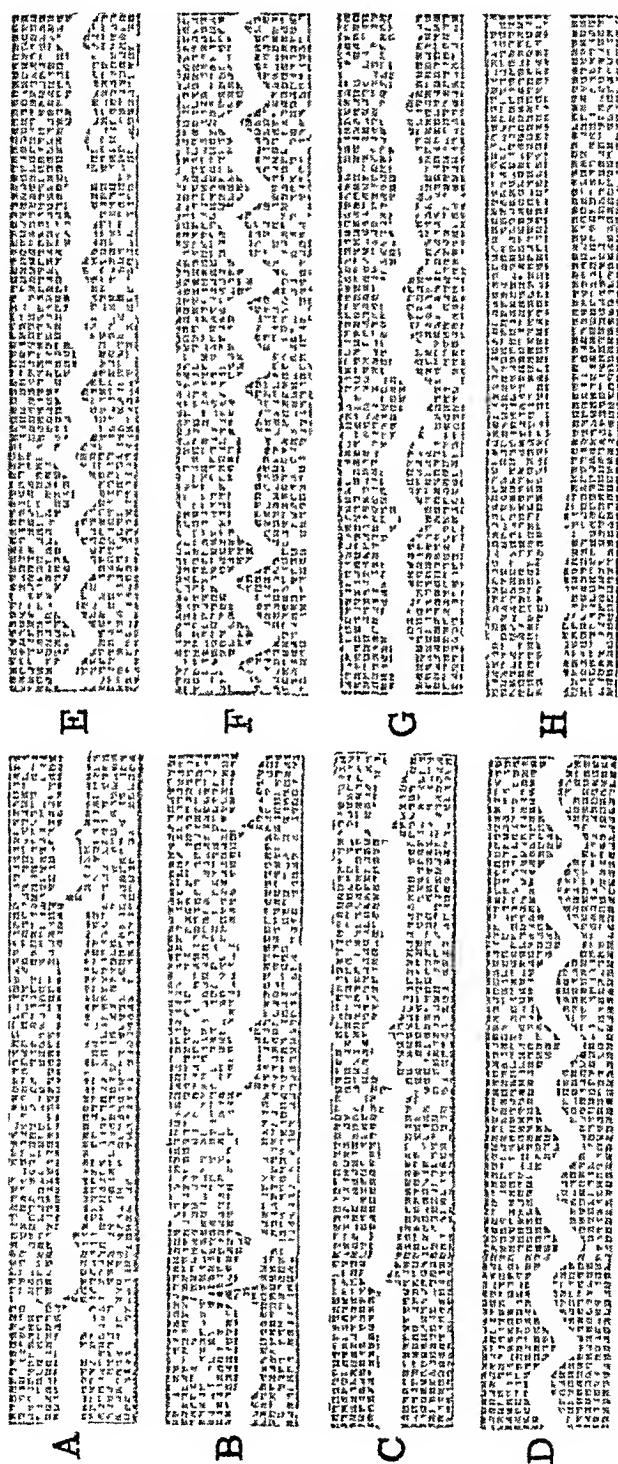


FIG. 10. Sequence of events in case 27. Lead II. A. Sinus bradycardia. B. Ventricular extrasystole. C. Idioventricular rhythm. D. Ventricular flutter. E. Ventricular fibrillation. F. Epinephrine given into cardiac chamber without effect. Epinephrine given into myocardium with resultant ventricular fibrillation shown in F, G, and H.

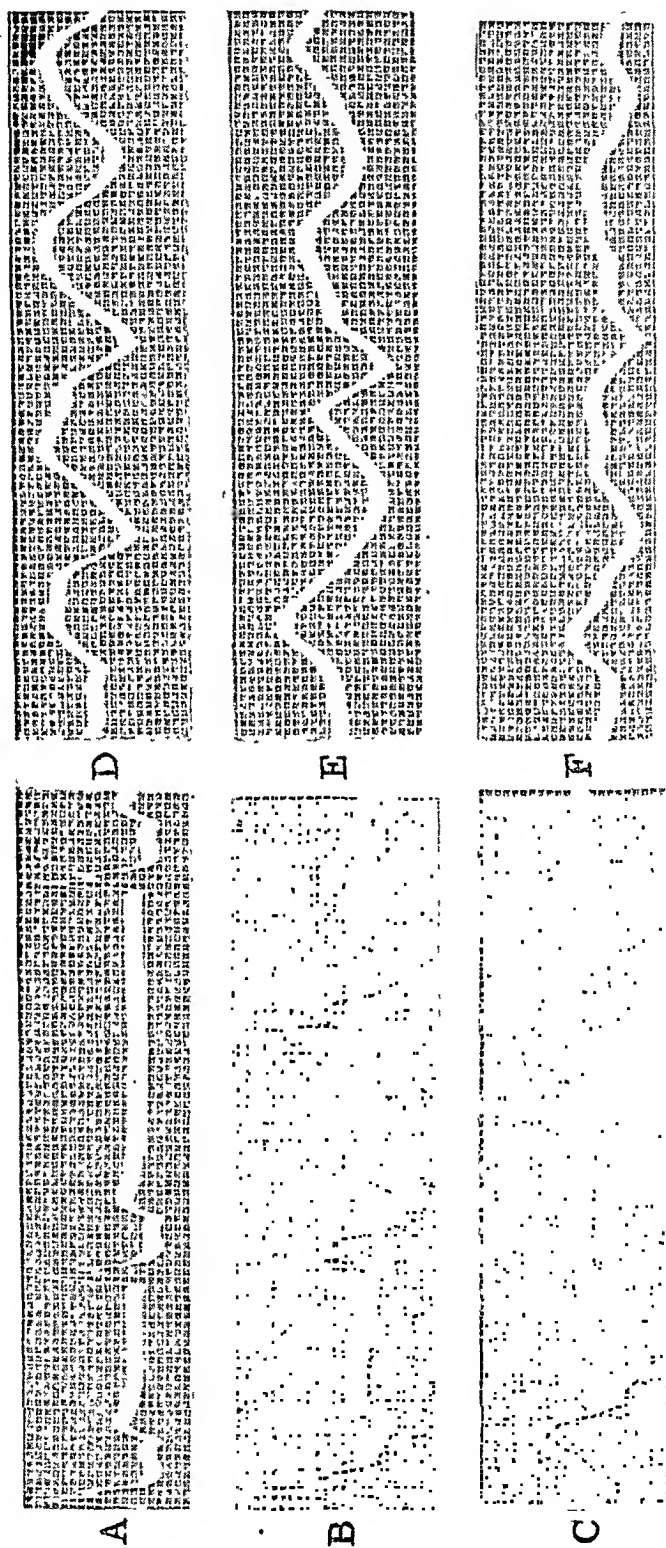


Fig. 11. Sequence of events in case 34. Lead II. A and B. Auricular fibrillation. C. Complete A-V block. D, E, and F. Epinephrine given into myocardium with resultant ventricular flutter and fibrillation.

in addition produce transient focal and local points of heightened irritability particularly in the ventricular myocardium and only infrequently in the auricular wall.

Intracardiac epinephrine following cessation of the cardiac beat produced only infrequent and usually insignificant responses. Only in seven of 18 patients so treated was there some sign of cardiac resuscitation and in five of these the effect was produced by myocardial infiltration and in two others by injection into the cardiac chambers. In only two of the patients was there a restoration of the original ventricular beats for a significant time whereas the others suffered the initiation of terminal ventricular fibrillation or ventricular extrasystoles. It appears not unlikely that if the patients in this series had not been so chronically and terminally ill, intracardiac epinephrine preferably given into the myocardium might have been more successful. Furthermore, unlike the procedure followed in this investigation it would appear that the intracardiac epinephrine to be life saving should be given if at all possible before complete cardiac cessation when the heart muscle and vital cerebral centers have not been deprived of oxygen for too long a period. Resuscitation otherwise becomes quite impossible because of the fatal and irreversible changes due to anoxemia.

### SUMMARY

Electrocardiograms were taken on 34 cases before, at the time of, and after clinical death. Slowing of the cardiac rate was almost a constant finding with subsequent sinoauricular node depression and resultant auriculo-ventricular nodal rhythm appearing in over one third of the cases. Auriculo-ventricular and intraventricular block in various degrees was extremely common. Evidences of ventricular irritability were manifested by the frequent occurrences of ventricular fibrillation, tachycardia and flutter along with ventricular extrasystoles from single and multiple foci. Auricular fibrillation did not appear terminally except in those instances where it had been present previously. The terminal complex in the electrocardiogram represented ventricular activity in 27 cases and auricular activity in seven. The terminal ventricular complexes often assumed bizarre shapes with marked variation in form, amplitude, duration, and with considerable slurring.

Attempts at cardiac resuscitation with intracardiac epinephrine following cessation of heart activity were made in 18 cases including 11 attempts in which the drug was injected into the cardiac chambers and nine in which it was infiltrated into the ventricular myocardium. The latter method was more successful, producing an effect in five cases (56 per cent) whereas the former accounted for only two responses (18 per cent). The resultant rhythms included three instances of ventricular fibrillation, and two of ventricular extrasystoles; in only two patients was there restoration of regular

ventricular beats in one of whom the cardiac activity continued for 36 minutes after respiration had ceased.

The authors gratefully acknowledge their appreciation to Miss Edna Edwards, Mrs. Dorothy Marsden and Miss Wanda Wilson for their technical assistance.

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# LABILE DIABETES: ELECTROENCEPHALOGRAPHIC STATUS AND EFFECT OF ANTICONVULSIVE THERAPY \*

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IN a study of spontaneous hypoglycemia associated with electrocerebral dysfunction<sup>1</sup> emphasis was laid on the similarity of symptoms in both conditions for which reason their coexistence may be overlooked. It was also shown that in such patients the clinical manifestations of hypoglycemia may develop in absence of critically low blood sugar levels, and it was assumed that when both conditions are operative in the same subject the threshold for the development of clinical reactions is decreased. Finally, it was found that the patients respond remarkably well to therapy which, in addition to management of hypoglycemia, includes the use of anticonvulsant medications.

The peculiar features of hypoglycemic reactions in labile diabetes, namely their frequency and severity and the suddenness of their onset, suggest a state of unusual reactivity to insulin or to fluctuations of the blood sugar and make it conceivable that factors other than mere depression of the blood sugar may be responsible for hypoglycemic manifestations in this type of diabetes. Thus a certain analogy could be drawn regarding the mechanism underlying the hypoglycemic complex in both spontaneous hypoglycemia and labile diabetes. With this idea in mind we have undertaken to study in the latter condition the configuration of the brain waves pattern as well as the relationship between insulin reactions and glucose concentration in the blood. We were also anxious to investigate the possible use of anticonvulsants in unstable diabetes.

The term "labile diabetes" has not been well defined in the literature. Its more or less synonymous use with the term "juvenile diabetes" stems from observations made in children whose diabetes is characterized by frequent incidents of hypoglycemia alternating with acidosis and coma. In this presentation the term labile diabetes refers to that group of diabetics who, regardless of age, time of onset and duration of disease, exhibit a very narrow time-margin between excessively high and critically low blood sugar values, and who in consequence show rapid transitions from hypoglycemia and aglycosuria to massive glycosuria and acidosis. In these patients small amounts of insulin used during episodes of heavy glycosuria often produce a rapid fall of the blood sugar to hypoglycemic levels; but if no additional insulin is given the sudden development of acidosis may not be averted.

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Clearly, labile diabetes is considerably distressing to the patient and its management imposes a great burden on the physician.

*Material and Procedure.* A group of seven labile diabetics with no family history of epilepsy and no history of convulsive seizures prior to the onset of diabetes, was studied. Blood sugar determinations and urinalyses for sugar content in casual as well as 24 hour specimens were made at least once a month. Whenever possible, blood sugar determinations were also done in the course of hypoglycemic manifestations or at the time the patients complained of signs of oncoming reactions. On several occasions the tests were repeated after an interval of one to two hours during which interval food was withheld in spite of subjective and objective signs of insulin reactions.

Electroencephalograms were taken by means of the three-channel Grass instrument. Both the bipolar and monopolar systems of recording potential variations from the brain were utilized. Electrodes were placed over the prefrontal, motor, parietal and occipital regions of the head bilaterally; indifferent electrodes were applied to the ear lobes. After a preliminary resting record was obtained patients were routinely hyperventilated for a period of two minutes. The criteria for determining abnormal activity depended upon the presence of slow potentials, high amplitude fast potentials and irregular or disorganized patterns. In order to avoid the effect of low blood sugar concentrations the electroencephalograms were taken after a normal meal (breakfast or lunch).

The effect of anticonvulsants was studied in three cases. Periods of five to 33 days during which anticonvulsive therapy was discontinued were interposed to serve as controls. Control electroencephalograms were taken in two patients after 12 and 17 months of treatment.

#### CASE REPORTS

*Case 1.* A 44 year old man, a college professor, was first seen in October 1942. He developed diabetes at the age of thirty-four. On a low carbohydrate, high fat diet with two doses of regular insulin daily he felt continuously weak and tired and had frequent insulin reactions alternating with glycosuria. Accused by his physicians of breaking the diet, he felt humiliated and compelled to do without medical advice. For eight years he made his own experiments in raising the dietary carbohydrates, but finally because of frequent insulin reactions and a state of constant fatigue he consulted a physician who prescribed a diet of 300 gm. of carbohydrates with an insulin dosage of 70 units of protamine-zinc and 14 units of regular insulin. On this regimen the patient felt somewhat better and gained some weight but his diabetes could not be satisfactorily regulated. From the very onset the patient's symptoms and laboratory findings were characteristic of unstable diabetes. He had frequent manifestations of an overdose of insulin ranging from mild paresthesias to severe reactions with retrograde amnesia, as well as periods of hyperglycemia accompanied by heavy glycosuria. To overcome reactions he took food in excess of the prescribed diet and was gaining weight constantly. In 1940, for instance, his weight rose from 137 to 163 pounds, a gain of 26 pounds in one year. He had a rapid pulse rate for years, but the basal metabolic rate was found on several occasions to vary from

minus 10 to minus 14 per cent, and the electrocardiograms were normal. There was also a change of personality manifested by extreme anxiety, depression, episodes of impulsiveness and restlessness as well as mental sluggishness which interfered with his professional work. To combat these neuro-psychiatric manifestations he took phenobarbital and B-complex capsules but because of lack of response he was finally given up as a case of hypochondriasis.

To prevent this patient from having his daily reactions a gradual reduction of insulin was made and he was placed on a constant diet of 230 gm. of carbohydrates, 70 gm. of protein and 75 gm. of fat. However, his diabetes remained uninfluenced and as chaotic as before. In January 1943, for instance, for a period of 10 days he was subject to reactions with only 40 units of protamine-zinc insulin, then developed marked glycosuria which necessitated an increase in the dosage to 48 units of protamine-zinc and 10 units of regular insulin. For short periods of time he seemed to be regulated on 40 to 54 units of insulin with a diet of 240 to 260 gm. of carbohydrates, while on other occasions reactions would increase in frequency and severity on as little as 8 or even 5 units of protamine-zinc insulin. The amount of sugar in the urine was also subject to considerable variation.

Because of frequent reactions, on three occasions it was necessary to take him off insulin for periods varying from three to 10 days. Strangely, even when no

TABLE I  
Blood Sugar Values during Reactions In Case 1

Date	First Blood Sugar Reading	Second Blood Sugar Reading 2 Hrs. Later
August 18, 1943	187 mg. per cent	
November 11, 1944	300 mg. per cent	214 mg. per cent
December 9, 1944	318 mg. per cent	200 mg. per cent
February 17, 1945	217 mg. per cent	187 mg. per cent
March 10, 1945	217 mg. per cent	178 mg. per cent
September 8, 1945	221 mg. per cent	148 mg. per cent
October 13, 1945	360 mg. per cent	190 mg. per cent
January 8, 1946	286 mg. per cent	226 mg. per cent

insulin was taken he still complained of reactions and continued to consume large amounts of carbohydrates. During one of these periods without insulin, for instance, he took one day in addition to his diet, some 400 gm. of carbohydrates seemingly without much effect.

The concentration of sugar in the blood also showed extreme lability with rises and falls occurring with great rapidity. However, a more detailed study of reactions revealed that clinical symptoms usually attributed to an excess of insulin frequently occurred at high blood sugar values. Readings obtained on several occasions while he exhibited moderately severe reactions are presented in table 1.

Throughout a period of four years different plans of insulin administration were used. The ones that seemed to yield some results at one time were usually found at another time to be of no benefit to the patient.

Because of the extreme lability of the patient's diabetes, and because his reactions seemed unrelated to blood sugar variations, an electroencephalogram was taken on June 17, 1946. This revealed several long bursts of 2 to 3 cycle per second activity over the right frontal area. Hyperventilation did not appreciably alter the pattern. The tracing was interpreted as suggestive of an epileptogenic focus in the right frontal area (figure 1).

The patient was first given for five days tridione which he did not tolerate well, then dilantin which he took continuously for four weeks. In the following five months, i.e., from the beginning of August to the end of December 1946, five control periods without dilantin varying from seven to 15 days were interposed. During

control periods he remained fairly well for only five to seven days. Whenever the test period was continued beyond a week reactions became quite frequent and distressing. On one occasion on the eleventh day without dilantin he "was up all night with definite shocks," took 50 gm. of carbohydrates without relief, reduced the insulin dose on the next day, but was unable to stop the reactions. Being very co-operative and much interested in this study, he was anxious to continue the experiment, but decided that he could no longer do without dilantin. The drug was re-

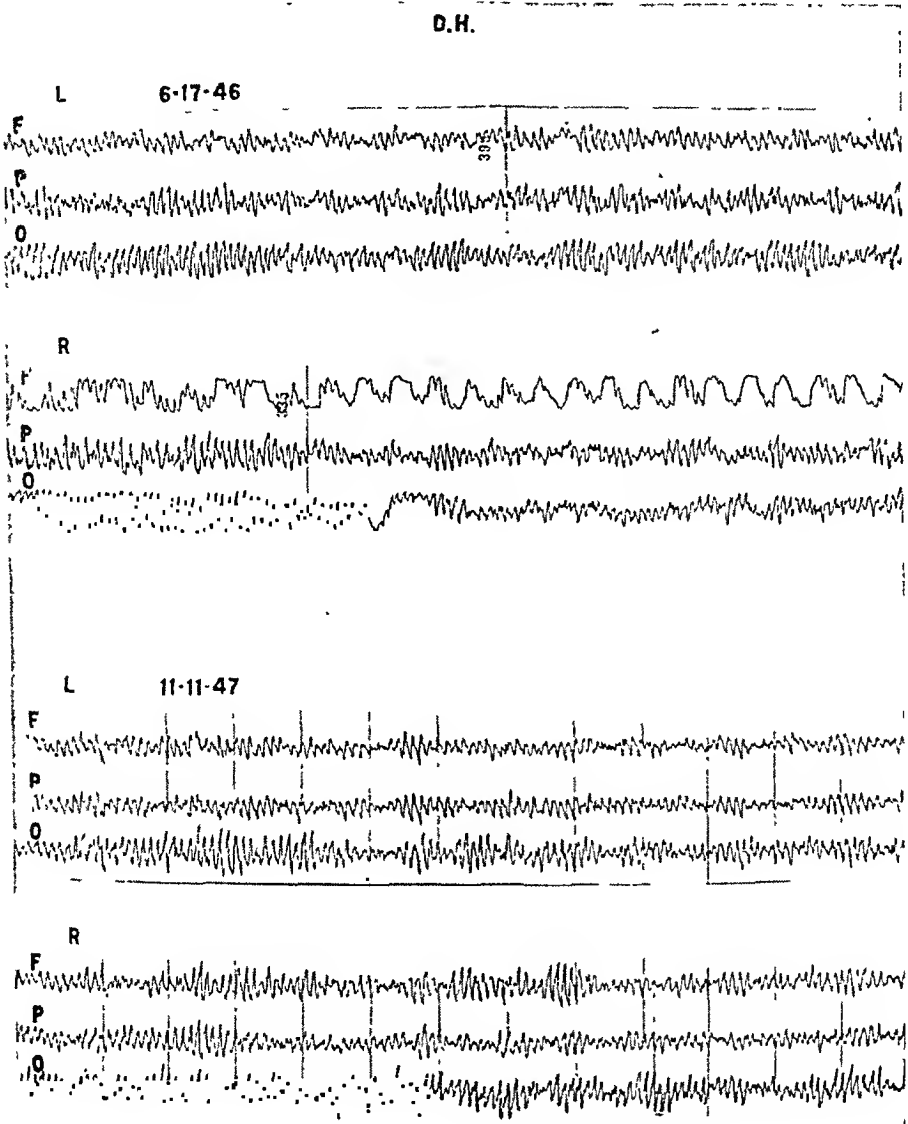


Fig. 1. Initial and control electroencephalograms in Case 1.

sumed on the twelfth day of the control period and the reactions became milder and less frequent and subsided entirely within three days. Recently dilantin was gradually replaced by mesantoin which for the past six months was taken for periods of 10 days with rest periods of three to five days. Except for drowsiness and a slight depression during the first two weeks on mesantoin the medication was well tolerated. The patient remains free from severe and moderately severe reactions and is subject

to infrequent and very mild reactions. Their onset is slow and gradual in contrast to their precipitous onset in previous years and they yield easily to small amounts of carbohydrates. He seems to be stabilized on 22 units of protamine-zinc and 20 units of regular insulin. Most of the time he is sugar free and his blood sugar is maintained in the normal range. Since the anticonvulsant treatment was initiated 14 blood sugar determinations showed variations from 120 to 200 mg. per cent and only on two occasions, when he had a cold, were higher values of 208 and 210 mg. per cent obtained.

To test his reactivity to low blood sugar concentrations, on one routine visit when his blood sugar was 120 mg. per cent food was withheld for two hours. He felt well during that time and exhibited no signs of reaction although his blood sugar dropped to 95 mg. per cent.

TABLE II  
Description of Experiences without Dilantin and during Dilantin  
Therapy as Reported by Case 1

Nature of Experience	Without Dilantin	While on Dilantin
Mild shocks	Frequent	Very few
Pronounced shocks	A few	None
Very sudden onset of shock	Frequent	None
Disturbance of vision	Frequent	None
Shock-like symptoms when number of urine tests show heavy sugar	Frequent	None
Associates' comment on unusual pallor or flush	Frequent	None
Periods of weakness and fatigue without previous exertion	Frequent	None
Sweating in absence of exertion	Frequent	None
Tingling sensation in hands and feet	Occasional	None
Cold hands and feet	Frequent	Seldom
Headaches	Occasionally	None
Boredom and drowsiness	Frequent	Seldom
Uncalled-for anger responses	Frequent	None
Self-pity tendencies	Frequent	Seldom
Pronounced anxiety	Frequent	None
Periods of impulsiveness alternating with indecisiveness	Frequent	Much more smoothed out
Elation alternating with depression	Frequent	Smoothed out
Tendency toward errors in various types of manipulations (e.g. mathematical work, speech, painting, writing, games, etc.)	Frequent	Seldom
Difficulty in beginning, or once begun persisting in work or recreation	Pronounced	Very mild
Background feeling	Uneasy— what's next?	Feeling of well-being

The patient also shows a remarkable psychologic improvement. His ability to work has greatly increased. He has regained confidence in himself and has no difficulty in carrying out his professional duties. He feels that the improvement evidenced in laboratory data "does not reflect the great improvement that has occurred. My inner report is much better than my charts."

A control EEG taken after 17 months of treatment shows a borderline tracing with no features suggestive of an epileptogenic focus. High voltage 8.5 to 9 cps rhythm dominates in all leads and only a few 8 cps potentials are observed (figure 1).

The favorable effect of anticonvulsive therapy in this case is best illustrated by the patient's own comparison of symptoms which he exhibited for years with the improvement noticed shortly after the treatment was begun (table 2).

Case 2. A young woman, aged 31, unmarried, developed diabetes at the age of twenty-four. The onset of her diabetes was extremely sudden, practically a matter of less than 24 hours with polyuria coming on unexpectedly one day and nocturia the

following night. The patient remembers distinctly that during that night she had to get up seven times to pass water. Her diabetes was diagnosed two weeks later. She was placed on a restricted diet with three daily injections of crystalline insulin. Within less than four months her weight dropped from 142 pounds to 119. She was then given a liberal diet with 300 to 390 gm. of carbohydrates, 95 to 130 gm. of protein and 60 to 100 gm. of fat, with a daily insulin dosage of 64 to 92 units of protamine-zinc and 9 to 18 units of regular insulin. On this regimen her weight rose rapidly to 155 pounds and she felt much stronger. From the beginning of insulin therapy she was subject to frequent severe reactions, particularly at night and upon arising in the morning. The reactions were often associated with loss of consciousness and she had to be fed sugar forcibly by her family. She was unable to work, became depressed, and although a very popular girl before she developed diabetes, she avoided people and lived almost like a recluse.

When first seen at the age of 26 her height was 70.5 inches and her weight 144.75 pounds. She complained chiefly of insulin reactions and extreme tiredness. Menstrual periods were delayed for two or three months and very painful. On one occasion shortly after the onset of diabetes, she had not menstruated for nine months. She often ran a series of insulin shocks during periods as well as during the time of anticipated and missed periods. Physical examination was negative except for hypotension and chronic acne of the face. The basal metabolic rate was minus 23 per cent. There was no family history of diabetes nor epilepsy, no history of head injury nor convulsions in the patient's infancy.

Because of frequent and incapacitating insulin reactions the patient was compelled to take extra carbohydrates almost every day. It was thought that with less insulin she might be able to avoid reactions and keep her diabetes under better control. To this end, in the first eight months of treatment insulin was gradually reduced to 42 units of protamine-zinc and 10 units of regular, while the diet was kept constant at 240 gm. of carbohydrates. However, in spite of the constancy of diet and insulin, she continued to have daily reactions alternating with heavy glycosuria. On one occasion, for instance, she was shocking all day, then suddenly before midnight developed polyuria with massive glycosuria. At another time a series of hypoglycemic reactions came on shortly after lunch and though she ate every half hour for some five hours, she remained sugar free with no relief from most severe headaches. An intravenous administration of glucose had no effect, and the headaches subsided

TABLE III  
Variations in Sugar Excretion during the Night in Case 2

Date	Amount of Sugar	Remarks
1943 November 13	61 gm.	Severe reaction on the previous day
27	12 gm.	Reaction at 11:00 a.m. same day
29	6 gm.	
30	10 gm.	
31	2.3 gm.	
December 30	5 gm.	
1944 January 20	0.7 gm.	
21	9 gm.	
22	±	
February 18	22 gm.	
March 19	4 gm.	Blood sugar 250 mg. %
21	38 gm.	
22	30 gm.	
23	3 gm.	
24	1.8 gm.	
26	11 gm.	
27	1 gm.	
April 1	24 gm.	

only after another glucose injection 20 minutes later. However, within a half hour heavy glycosuria appeared, so that scarcely an hour after the intravenous administration of glucose she had to be given insulin.

Since the most serious reactions occurred upon arising, to prevent them the morning glycosuria had to be tolerated. Urine specimens covering the period from bedtime until morning showed great variations in sugar content as may be seen from table 3. The sugar excretion during the day was also most irregular. On some days she remained sugar free the whole forenoon while on others the urine was loaded with sugar. At times her diabetes improved for no apparent reason so that for a few weeks there was little sugar in the urine and only a few mild reactions.

Blood sugar specimens usually taken one and a half to two and a half hours after breakfast showed over a period of three and a half years a wide range of variations from 95 to 378 mg. per cent. Also, there was no parallelism between the blood sugar values and the amounts of sugar excreted as may be seen from table 4.

Just as her diabetic condition, so also her weight showed marked fluctuations. At times it remained stationary for months; then for no demonstrable cause it would drop in a few days by 8 to 10 pounds and remain again unchanged for weeks or months.

Various insulin mixtures were used without much effect, and the only valuable result was obtained by a reduction of the morning insulin dose so that additional insulin could be taken during the day if necessary. In this way the patient was able at least to keep free from severe shocks on arising. In November 1944 globin insulin was given a trial. At first she had globin insulin alone, but soon to check the heavy

TABLE IV

Comparison of Blood Sugar Values with the 24 Hr. Sugar Excretion in Case 2

Date	Blood Sugar	Sugar in 24 Hr. Specimens
1942 October 30	142 mg. %	25 gm.
1943 April 17	166 mg. %	29 gm.
July 2	220 mg. %	115 gm.
August 3	250 mg. %	6.6 gm.

morning glycosuria protamine-zinc insulin was added very cautiously. A dosage of 20 to 22 units of protamine-zinc with 20 to 22 units of globin insulin was finally adopted and in addition she took regular insulin during the day whenever necessary. On this regimen she felt more secure although her diabetes remained basically unchanged. She still had to take up to 38 additional units of regular insulin on some days and none on others, and she continued to show sudden changes from hypoglycemic reactions to hyperglycemia with massive excretion of sugar and extreme exhaustion.

Gynecological examination by two competent specialists revealed no pelvic disease. To control the dysmenorrhea and oligomenorrhea they suggested various combinations of hormonal therapy. We tried estrogens by mouth and parenterally, luteal hormone alone or in conjunction with estrogens (Dipro), gonadotropin, and thyroid extract in a dose of one half to two grains a day. The response of her diabetic condition to hormonotherapy was most chaotic. On stilbestrol, for instance, the insulin requirement was reduced and the frequency of reactions diminished on some occasions, while on others there was heavy glycosuria accompanied by tiredness and loss of weight. Corpus luteum therapy usually caused an increase in glycosuria, whereas Dipro injections were followed by glycosuria and polyuria, except for one instance when there was less spilling of sugar on Dipro.

Likewise, no constant relationship could be found between menstrual periods and the diabetic state. Most of the time she ran a series of reactions during the first few menstrual days, but in June 1944 she required more insulin during the first menstrual

day and much less on the last day of the period as well as during two postmenstrual days. At times hypoglycemic manifestations came on during the six to ten premenstrual days and were succeeded by glycosuria and increased insulin requirement at the onset of the period and by recurrence of reactions at the end. At other times heavy glycosuria preceded the period by three days, necessitating almost double the usual amount of insulin. On the whole, the insulin requirement around and during the periods changed most rapidly and unpredictably. On one occasion, for instance, while she was doing relatively well for some 10 days on 20 units of protamine-zinc and 34 units of regular insulin with additional 5 to 6 units of regular insulin in the afternoon, she excreted large amounts of sugar on the first menstrual day, had continuous reactions all of the second day, again needed more insulin on the third day. Then she felt fairly well for the next three days, but reverted to heavy glycosuria during the three postmenstrual days.

On June 26, 1946, an electroencephalogram was taken. The tracing showed moderate voltage 10 cps alpha rhythm with occasional trains of low to moderate amplitude fast activity and some irregularities in wave contours. Hyperventilation resulted in a few 6 to 8 cps potentials. The record was reported as a borderline tracing.

Tridione was chosen as the first anticonvulsant drug to be tried in this case. After a preliminary period of 11 days during which the patient had only one mild reaction and needed additional 6 to 8 units of regular insulin on three days, the drug was given for seven days, namely, from the sixteenth to the twenty-second intermenstrual days. While taking tridione she had several mild reactions on the first day and frequent severe shocks without loss of consciousness on the second, fourth and fifth day. A marked glycosuria occurred on the third, sixth and seventh days and could not be controlled even with 30 additional units of regular insulin. The patient felt very depressed and so weak that she could hardly get out of bed. From the third day on tridione she felt blinded in the sun and had the sensation of seeing objects lose their shape and identity in an intense blur of light. On the whole, on tridione she was decidedly worse—"never in my whole life have I felt so rotten."

Dilantin was begun 11 days after the next menstrual period, after a lapse of 17 days during which heavy glycosuria occurred only once. The drug was taken continuously for 55 days. During the first 42 days there were only two mild reactions and only small additional doses of insulin (from 8 to 10 units) were needed on nine days. During the next menstrual period she had three mild reactions and no additional insulin was required. Then because of intermittent aphthous stomatitis dilantin was discontinued and soon the rate of reactions increased and additional doses of insulin were more frequently used. After 48 days without dilantin the drug was resumed, and for over nine months it was taken regularly for periods of 10 to 17 days with rest periods of five to seven days. During the first few days on dilantin the need for insulin was markedly reduced and she had four severe reactions followed by glycosuria of one day's duration. But soon thereafter her diabetes seemed to be more stabilized with few mild reactions and infrequent incidents during which 6 to 8 additional units, and only once 10 units of regular insulin were needed. On several occasions she remained entirely free from reactions for over three weeks. During two control periods of 10 and 32 days without dilantin, only a few mild reactions occurred near the menstrual periods (four mild and one moderately severe reaction during the one month control period). The insulin requirement remained more stable even in the course of menstrual periods.

Dilantin proved particularly valuable for the control of reactions. During a six months' period before the treatment was begun, the patient had a total of 48 days in which reactions occurred, while in the six months' period with dilantin 25 such days were noted. During the same six month period there were 17 severe reactions



when no medication was taken, as against four severe reactions since the treatment with dilantin was inaugurated. Furthermore, on dilantin the onset of reactions was smoothed out and gradual so that the patient found it easier to cope with them, while before this therapy reactions occurred mostly without warning and rapidly grew deep.

The effect of dilantin on the blood sugar was also significant. Of 15 determinations, 13 showed variations from 107 to 200 mg. per cent; one was 245 mg. per cent on the third day of menstruation and another one 235 mg. per cent two days after a period. An improvement was also noted in the patient's general condition. Her weight rose to 143 pounds and remained stationary for over nine months. She also shows a good psychologic adjustment. In her own words "dilantin is a miraculous drug."

In the past three months the patient was gradually changed over to mesantoin with results as good as those obtained with dilantin.

*Case 3.* A married woman aged 33 years, a writer by profession, was first seen in September 1942. She was well until 1940 when because of her mother's death and her husband's business difficulties she became greatly depressed, lost interest in her family, and began to lose weight rather rapidly (she recalls losing some eight pounds in one week). A psychiatrist advised psychoanalytical treatments, but the patient could not accept the idea that she herself would be unable to overcome her personality disorders. As her condition did not improve, three months later she submitted to psychoanalysis. Supposedly two days after the first treatment she developed polyuria and nocturia and shortly thereafter sugar was found in the urine. At first she was placed on a 900 calorie diet, but continued to lose weight, felt weak, and had bouts of excessive perspiration. Pulmonary tuberculosis was then suspected but ruled out in view of negative laboratory findings. At the end of the first year of treatment her diet was slightly enlarged and she was given 5 to 10 units of regular insulin daily. She soon began to suffer from frequent insulin reactions, was unable to attend to her work and was on the verge of suicide. She then consulted another physician and was given a diet of 250 gm. of carbohydrates, 80 gm. of protein and 70 gm. of fat, with 36 to 40 units of protamine-zinc and 10 to 14 units of regular insulin daily. Her diabetic difficulties can be summed up as follows: She was afraid of glycosuria and tried hard to keep her urine sugar free. In this she was not successful as the addition of small amounts of insulin (4 to 8 units) to combat a heavy glycosuria would bring on reactions within a few hours. In consequence, there were periods of sugar free tests accompanied by continuous tiredness and frequent moderately severe insulin reactions interspersed with periods during which she excreted large amounts of sugar. On several occasions the 24 hour specimens contained up to 60 gm. of sugar and more. During the premenstrual week she always had more sugar in the urine and felt extremely tired, nervous and depressed, frequently had a feeling of inward trembling and tightness in the neck, and her sleep was restless. With the onset of menstrual bleeding these symptoms would subside and frequent reactions would appear even with a reduced insulin dosage. She learned to take more insulin before her periods and lower the dose markedly with the onset of the flow, but even so she was unable to control the described sequence of events. She also gave a history of anxiety for which she had been psychoanalyzed for the past three years.

Thirty-three blood sugar determinations made between September 1942 and October 1946 showed variations from 127 to 260 mg. per cent. On two occasions the blood sugar concentration was low (69 mg. per cent); on one occasion it reached 308 mg. per cent. In September 1946, for no apparent reason insulin reactions became more frequent and severe; they lasted longer than usual and did not yield easily to ingestion of carbohydrates. At this point (September 30, 1946) an electroencephalogram was taken. This revealed moderate to high amplitude 11 cps rhythm

with some admixture of fast activity. There were frequent random 6 to 8 cps potentials and occasional 5 cps potentials. Hyperventilation produced hypersynchronous discharges of 5 to 6 cps rhythm in all leads. The tracing suggested a generalized cerebral disturbance of physiologic nature, but it could also be considered as consistent with a convulsive tendency (figure 2).

Dilantin was then prescribed for periods of 10 days with rest periods of five days and the patient improved considerably. There was a better adjustment to insulin

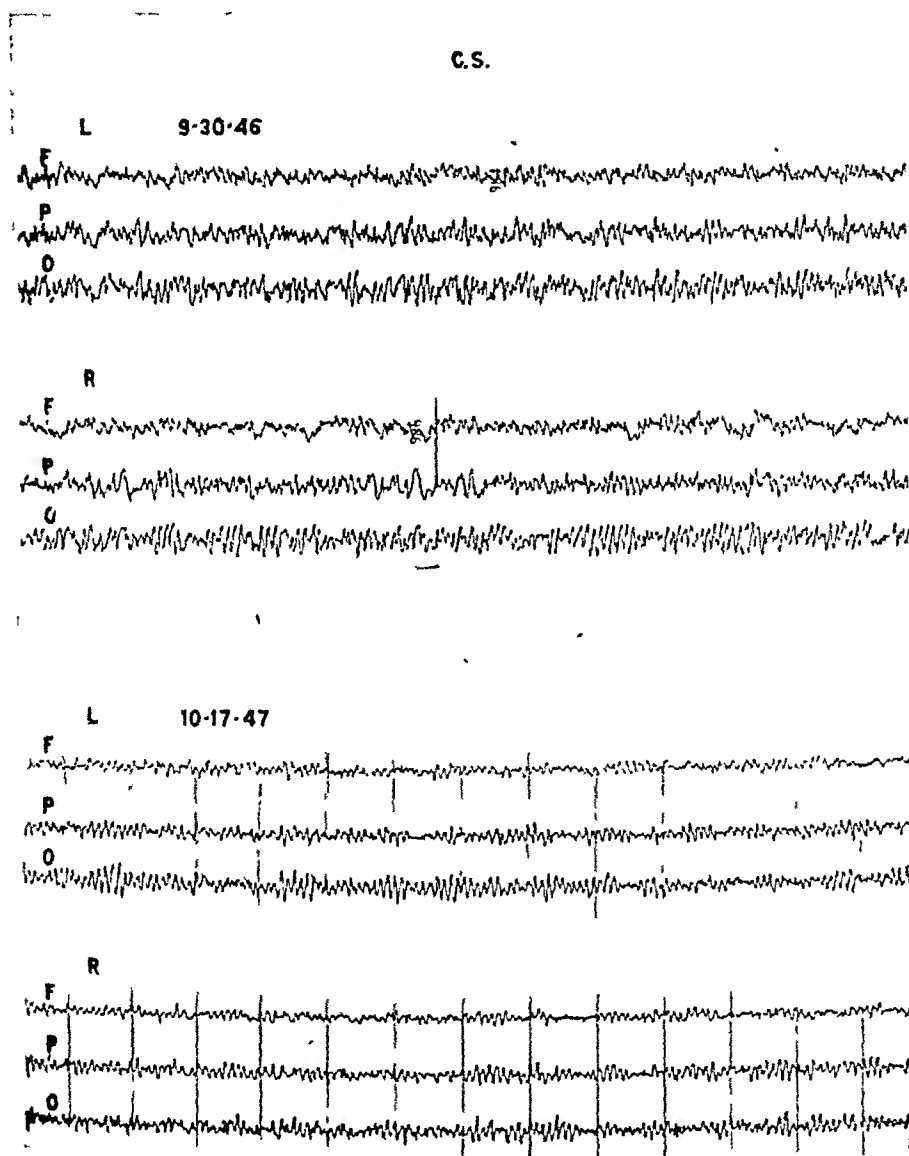


FIG. 2. Initial and control electroencephalograms in Case 3.

as evidenced by absence of reactions although the dose of insulin remained practically unchanged. In the patient's own words, she is now "less sensitive to insulin, not so prone to insulin reactions, and has a feeling that her diabetes is now a controlled thing." The premenstrual tension, depression and heavy glycosuria have also subsided. Moreover, she shows a remarkable psychologic improvement. She feels less restless, mentally more even, and has "far less anxiety in approaching things

in general." In the past 12 months during which dilantin was taken, the blood sugar concentration varied from 80 to 182 mg. per cent; on one occasion it was 61 mg. per cent and on another 236 mg. per cent. In November 1946 she took no dilantin for 10 days and her blood sugar rose to 266 mg. per cent. Again, she was without the medication for 14 days in February 1947 and in the last six days of that period her nervousness recurred and the reactions became quite frequent. A control electroencephalogram taken in October 1947 showed no definite abnormality. It was free from previously noted random 5 to 8 cps potentials and hyperventilation resulted in only a few 7 to 8 cps potentials (figure 2).

## COMMENT

1. *Correlation between Clinical Reactions and Blood Sugar Values.* A certain proportion of reactions noted by our patients were due to the hypoglycemic effect of insulin and yielded to oral administration of carbohydrates or intravenous injection of dextrose. However, in an appreciable number of instances the patients were unable to combat reactions even with considerable amounts of carbohydrates and the reactions continued for unusually long periods of time. Moreover, they coincided with moderate or heavy glycosuria. A study of glucose concentration in the blood during such unusual reactions was undertaken in Case 1 and revealed surprisingly high values. During the two hours of observation the blood sugar failed to fall to pathologic low levels and neither intake of carbohydrates nor abstinence from food had any effect on the course of reactions.

The symptom-complex which accompanies various types of experimental or clinical hypoglycemia is not always well correlated with the depression of the blood sugar. Appreciably low blood sugar levels may remain asymptomatic<sup>2-14</sup> while the hypoglycemic symptom-complex may be encountered in absence of critically low blood sugar concentrations.<sup>1, 4, 15-19</sup> Various theories have been offered to explain this lack of parallelism between the clinical and laboratory status of hypoglycemia. The one that has gained wide acceptance is that hypoglycemic reactions occur when the blood sugar falls rapidly even though a pathologically low level may not be reached.<sup>6, 13, 15, 20, 21</sup> However, the fact that a rapid fall of the blood sugar from very high to distinctly hypoglycemic levels is not always accompanied by symptoms<sup>6</sup> as well as the fact that critically low levels may remain asymptomatic negate the value of the assumption that hypoglycemic symptoms are produced by a sharp drop in the blood sugar level. Recently in discussing our paper on hypoglycemia, Himwich suggested that hypoglycemic manifestations may result from a low brain sugar which might not be reflected in the systemic blood.<sup>22</sup> In extension of this concept it is conceivable that even with normal availability of glucose in the brain there may be some disturbance in the uptake or utilization of sugar by the brain, thus depriving this tissue of its main nutritive substance.

The blood sugar readings obtained during reactions in our Case 1 are exceedingly high and we think it improbable that the hypoglycemic complex

could have developed with such high levels. On the other hand, the levels remained high for at least the two hours of observation, so that steepness of drop of the blood sugar as a factor productive of the clinical symptomatology can also be discarded. As for the possibility of an inadequate supply of sugar to the brain or some disturbance in its utilization by the brain, one can only theorize since at present there are no available data on the sugar content of human brain nor on the precise mechanism of the intermediary carbohydrate metabolism in the central nervous system. Another explanation which could account for such unusual reactions will be offered in the latter part of this presentation.

2. *Electro-Cortical Dysfunction.* Of the seven patients with labile diabetes, only one had a normal initial electroencephalogram. The abnormalities recorded in the remaining six patients can be grouped as follows: Low to moderate voltage fast activity was noted in three cases (among them Case 3); occasional sharp formations and spike potentials in two cases (among them Case 1); irregularities in wave contours in one case (Case 3); and slow 2 to 3 cycle per second activity in one case (Case 1). Hyperventilation did not alter the electroencephalographic pattern in four cases, and in others resulted in a few high voltage 5 to 8 cps potentials. These electroencephalograms were interpreted as borderline tracings in three patients, as consistent with convulsive tendency in two patients (among them Case 3) and suggestive of an epileptogenic focus in Case 1 (figure 1).

As mentioned earlier, to avoid a possible effect of low blood glucose concentrations on the electroencephalographic pattern the recordings were made after a normal meal and only at a time when the patients exhibited no subjective nor objective signs of hypoglycemic reactions.

In a study of spontaneous hypoglycemia in association with electrocerebral dysfunction<sup>1</sup> the electroencephalographic abnormalities were found not to be correlated with the blood sugar variations and it was concluded that the disturbed cortical activity did not represent a cerebral reaction to low blood sugar concentrations. Similarly, in the group of labile diabetics herein presented, deviations from the normal electroencephalographic pattern occurred in absence of low blood sugar levels and in consequence cannot be ascribed to the effect of the injected insulin. This is particularly well demonstrated by Case 1. On anticonvulsive therapy this patient was able to step up the dosage of insulin appreciably. He obtained better control of his diabetes, his blood sugar was reduced to normal levels, and yet reactions which were so frequent before anticonvulsive therapy was instituted disappeared almost completely.

Another question that may be raised is whether the reactions were not related to the diabetic condition per se. Greenblatt et al.<sup>23</sup> have recently reported on the occurrence of electroencephalographic abnormalities in diabetics with severe insulin reactions. The writers do not seem to consider the abnormal brain waves as secondary manifestations of repeated insulin reactions or of the diabetic state as such. Of great significance in this con-

nection may also be the fact that we were able to record disordered electroencephalographic patterns in several non-diabetic blood relatives of our patients. Thus a disturbed brain wave test was obtained in a sister of Case 2 as well as in a sister of another patient and two daughters of still another patient with labile diabetes and electrocortical dysfunction; but in contrast to the patients with labile diabetes, their relatives were suffering from spontaneous hypoglycemia. Since electroencephalographic abnormalities may occur in members of the same family with such opposed disturbances of the carbohydrate metabolism as diabetes and spontaneous hypoglycemia, it ensues that the abnormal cortical potentials cannot be correlated with diabetes as such. It is conceivable that they may be rather genetic in origin, but of course our observations are too scanty to justify any conclusion to this effect. Another point of importance is the improvement noted in control electroencephalograms obtained in patients 1 and 3 after prolonged administration of anticonvulsants (figures 1 and 2). This fact too may be taken to mean that the disturbance of cerebral electroactivity originally recorded in these patients was not produced by their diabetic condition as such.

3. *Nature of Reactions. Hypoglycemic and Pseudohypoglycemic Reactions.* Being aware that a number of their distressing symptoms are known to be usually associated with low blood sugar values, our patients have ascribed all their reactions to an overdose of insulin and have applied the common measures to combat insulin reactions. These, however, in a large proportion of reactions proved ineffective, and blood sugar determinations made in the course of such refractory reactions gave surprisingly high readings.

It becomes necessary then to consider what constitutes a hypoglycemic reaction. To a clinician, a reaction is thought of in terms of clinical symptoms which are assumed to result from abnormally low blood sugar levels or, in their absence from an abrupt fall of the blood sugar. Our observations, however, indicate that two types of reactions may exist in labile diabetes, one which is produced by hypoglycemia and responds to carbohydrate administration, and another which may develop even with high blood sugar values and is uninfluenced by carbohydrate therapy. Since the latter may be completely controlled by anticonvulsive therapy, it may be assumed that it is brought about by a disturbance of cerebral function which is independent of the concentration of sugar carried by the blood to the brain. Greenblatt et al. in their above quoted work have expressed the opinion that severe reactions in labile diabetes are due to both the unstable carbohydrate regulation and the unstable cortical function. They have thus called attention to the possibility that the distortion of the normal electroencephalographic pattern may be significant in the production of insulin reactions, but they failed to determine the exact position of abnormal brain waves in the mechanism of reactions in labile diabetes. Our studies, by separating the two varieties of reactions, form the basis for a dual theory

of reactions. According to this concept one group of reactions is produced by cerebral glycopenia, i.e., by disturbances in supply of glucose to or its utilization by the brain; the other group by disturbances in cerebral function which may arise with a normal or even an overabundant supply of glucose to the brain. It may therefore be suggested that the term of hypoglycemic or insulin reactions be reserved for reactions which are actually produced by hypoglycemic blood sugar concentrations, and the term of pseudohypoglycemic reactions be applied to those which develop in absence of actual hypoglycemia. The differentiation between the two varieties of reactions cannot be made on the clinical basis, but their delineation can be made easily with the aid of laboratory data, namely, the blood sugar determinations during attacks and the electroencephalographic study of the patient. The differentiation can also be supported by the therapeutic use of anti-convulsants..

The distinction between the two varieties of reactions appears to be of considerable practical importance. Since clinical manifestations in both types of reactions are indistinguishable, a pseudohypoglycemic reaction may be improperly taken for an insulin reaction and treated as such. The intake of large amounts of carbohydrates, although ineffective in warding off such a reaction, must unavoidably increase the magnitude of hyperglycemia and glycosuria and thus aggravate the diabetic condition. On the other hand, correction of the electrocerebral dysfunction may greatly facilitate the management and improve the outlook and the course of the disease.

Another point of importance is that the disturbed cortical function may intensify an actual insulin reaction or modify its character. Thus before the use of anticonvulsants, reactions in patients 1 and 3 were extremely sudden in onset and showed marked resistance to carbohydrate therapy, whereas on anticonvulsant therapy there were premonitory symptoms, the reactions grew slowly and their intensity was decreased.

4. *Dosage and Effect of Anticonvulsant Therapy.* Three drugs were used in an attempt to influence the cerebral dysfunction, namely, tridione, dilantin and mesantoin.

Tridione was administered to two patients (Cases 1 and 3) but because there was immediately a significant increase in the rate and severity of reactions and because of distressing side effects, the drug had to be discontinued after five to eight days of trial. Since tridione is known to aggravate epileptic symptoms temporarily, it appears possible that in our cases with a more prolonged administration the results ultimately would have been more satisfactory. Further study to determine the usefulness of tridione in labile diabetes seems indicated.

Very favorable results were obtained with dilantin which was administered to all three patients, as well as with mesantoin which was used in two patients. The drugs were given for periods of 10 days with rest periods of five to seven days. For the sake of observation, on some occasions the administration of dilantin was continued for up to 55 days and long control

periods were interposed. During the initial period of treatment the patients responded within 24 hours after the first dose, but later when the drug was readministered after control periods, three or four days were usually required to obtain relief. The improvement was maintained as long as the drug was given and continued on the average up to five days after cessation of therapy. Temporary discontinuation of administration produced no side effects and caused no aggravation beyond that observed before the therapy was inaugurated.

The daily dose of dilantin and mesantoin depended upon the evidence of clinical improvement. On the whole dilantin was given at the rate of 3 to 5 capsules a day and mesantoin in doses of 2 to 3 tablets daily. No undesirable side effects were noted except for bleeding from gums in Case 1 while on dilantin, but this could be controlled with oral administration of vitamin K so that the treatment did not have to be discontinued.

The response to the two anticonvulsants was excellent in two cases (Cases 1 and 2) and less favorable but definite in the third case. The results obtained can be summed up as follows:

(A) *Effect on Reactions.* The drugs have reduced the rate of reactions remarkably. In Case 2 the total number of days with reactions in a six month period prior to the use of dilantin was 48, while on dilantin it dropped to 25. Under this therapy the patient repeatedly remained without an attack for a period of over three weeks, which is the longest free period from the onset of her diabetes. There was an almost complete disappearance of reactions in Case 1 both on dilantin and mesantoin, and in Case 3 in which only dilantin was used. Of great significance is also the complete freedom from reactions at night in Cases 1 and 2.

Although with the aid of anticonvulsants the blood sugar values were reduced to a more physiological range the intensity of reactions was also favorably influenced. Patient 1, for instance, had no recurrences of severe and moderately severe attacks and experienced mild symptoms only at meal-time. Patient 2 was free from attacks on arising although her morning specimens for weeks were sugar free.

Lastly, the onset of reactions which was precipitous before the drugs were administered became smoothed out and gradual so that patients had time to apply proper measures before the reactions could grow deep. This was particularly appreciated by patients 1 and 2.

(B) *Effect on Hyperglycemia and Glycosuria.* As a result of the improvement in the rate and intensity of reactions the use of additional excessively high carbohydrate feedings was eliminated and in consequence hyperglycemia with glycosuria which usually followed reactions was prevented. Also, since the patients were able to adhere to their basic diets, the excretion of sugar was reduced and it was less subject to rapid variations. Remarkable, too, was the subsidence of premenstrual glycosuria in Case 3.

(C) *Effect on Insulin Requirement.* Because of severe reactions which in labile diabetes may follow the administration of even small amounts of

insulin, high blood sugar concentrations and glycosuria cannot be prevented and as suggested by Wilder, in such patients "aglycosuric urine should be carefully avoided."<sup>13</sup> Anticonvulsants proved very valuable in overcoming this difficulty. With their aid we were able, in the initial period of treatment, to step up the dosage of insulin safely and without the risk of reactions. As soon as the blood sugar level was lowered, the number of days with spilling sugar markedly reduced and the need for additional amounts of insulin to cope with unexplained bouts of glycosuria eliminated, it became possible to carry out the program of decreasing the insulin dosage. This is best illustrated by Cases 1 and 2 where after a preliminary increase in insulin we were able to effect an appreciable reduction in the basic requirement of insulin.

(D) *Effect on Behavior Disorders.* The personality disorders in labile diabetes may be related to the unstable character of this condition and the inherent difficulties in its management as well as to the distortion of the electrocerebral activity in some of such patients. These patients are anxious to keep sugar free but dread the incapacitating reactions. If they remain sugar free through the continuous and of necessity excessive use of insulin, they develop a state of constant hypoglycemic anxiety which is often mistaken for psychoneurosis, hysteria, etc. If, on the other hand, glycosuria cannot be avoided, they live in fear of diabetic complications and are apt to develop a feeling of guilt. Suspected by their physicians of breaking the diet and lack of honesty or stigmatized as neurotics or hypochondriacs they feel humiliated and lose faith in the medical profession. Humiliation, feeling of guilt and helplessness are indeed frequent accompaniments of labile diabetes.

In those in whom electroencephalographic abnormalities are present, the cerebral dysrhythmia may possibly contribute or predispose the individual to behavior disorders. Of interest in this connection might be the recently reported beneficial results obtained with anticonvulsant medications in problem children with electroencephalographic abnormalities.<sup>24</sup>

Under anticonvulsive therapy all three patients studied showed a remarkable psychologic improvement. As soon as the incidence and intensity of reactions were reduced, the fear of reactions abated. Subsidence of heavy glycosuria, on the other hand, has relieved the patients from fear of diabetic complications. With stabilization of diabetes, the anxiety, nervous tension and irritability were alleviated, the ability to concentrate and to work increased and as a corollary the patients exhibited a general feeling of well-being. A rather startling effect was obtained in Case 3. The severe premenstrual depression coinciding with large excretion of sugar which this patient experienced for years and which was unresponsive to insulin therapy was successfully influenced by anticonvulsive medication.

It is of interest to note that although some of the patients may have had personality disorders not related to their diabetes or to alterations of the



electroencephalogram, psychotherapy of itself which was applied in Case 3 was of no appreciable value to the patient.

### CONCLUSIONS

1. A group of seven labile diabetics with no family history of epilepsy, and no clinical evidence of epilepsy, was studied. A normal electroencephalogram was obtained in one patient and abnormal or borderline tracings in the other six. Of the latter, three were treated with anticonvulsants for a period of 13 to 17 months.

2. The electroencephalographic abnormalities recorded in this group of patients were shown not to be due to the effect of administered insulin, and they were assumed not to be related to the diabetic condition per se. A possibility of a genetic or constitutional factor responsible for these electroencephalographic alterations was suggested.

3. It was shown that reactions usually associated with insulin hypoglycemia may occur in labile diabetes at the time of exceedingly high blood sugar readings. Such reactions were found to be refractory to carbohydrate therapy, but were favorably influenced by anticonvulsive therapy.

4. A dual theory of reactions in labile diabetes associated with electrocerebral dysfunction was proposed. According to this concept, reactions were separated into two varieties, namely, virtual hypoglycemic reactions which respond to carbohydrate therapy and pseudohypoglycemic reactions which occur with normo- or hyperglycemic values and remain uninfluenced by carbohydrate administration.

5. Two anticonvulsants, namely, dilantin and mesantoin proved highly effective in the management of the patients studied. With improvement of diabetes under this therapy there was also a remarkable psychologic improvement. A return of the EEG to normal in the course of treatment was noted in two patients. Toxic reactions with the two anticonvulsants used were practically absent.

6. The importance of electroencephalographic studies in labile diabetes was pointed out. The recognition of cerebral dysfunction in this type of diabetes may aid in differentiating the two types of reactions and in consequence it may be translated into therapeutic terms.

7. Although the number of patients suffering from labile diabetes in whom anticonvulsants were studied has been small, and observations have extended for a little more than a year, the percentage and the magnitude of satisfactory results were appreciable. These results suggest the use of anticonvulsants as an additional and very valuable therapeutic measure in the management of labile diabetes.

*Note:* Since this paper was submitted for publication another of this group of patients was given mesantoin for a period of 10 months. Subjective and objective improvement was noted even though the insulin dosage was markedly increased. On the other hand, no effect was obtained in the only patient of this group who had a normal EEG. He was given mesantoin on the assumption that he may have a disturbance in electrocortical activity not reflected in the EEG. He took the drug for six weeks.

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# CONDITIONS TO BE DIFFERENTIATED IN THE ROENTGEN DIAGNOSIS OF PULMONARY TUBERCULOSIS \*

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THE use of roentgenology as an aid in the diagnosis of chest disease is now standard medical practice. Conservative physicians, be they internists, radiologists or chest specialists, are well aware of the fact that the bacteriological origin of the disease which produces a shadow in the roentgenogram cannot be determined from the roentgenogram alone. This important fact is sometimes lost sight of, especially by enthusiastic proponents of mass chest roentgen-ray surveys.

In order that physicians may have a convenient reference list of diseases, disorders and anomalies which may resemble pulmonary tuberculosis in the roentgenogram, that is, which may cast shadows identical with those cast by pulmonary tuberculosis in its various forms, this short article is being presented.

It is realized that some of the conditions listed are quite uncommon. Nevertheless, when millions of persons are being examined radiologically every year, occasional instances of these rarer lesions will arise, and their elucidation will be aided if the patient does not start off with an incorrect diagnosis of tuberculosis and then has to be reorientated to the correct diagnosis.

The use of properly performed skin tests, sputum examinations, gastric washes and cultures is too well known to need description here. The fact that hemoptysis is more common in bronchiectasis than in pulmonary tuberculosis is fairly well appreciated. But the fact that, as in all laboratory tests, an occasional false positive roentgenogram may be obtained is not sufficiently known by clinicians and public.

The author has seen examples of all of the conditions listed during some 21 years of radiological practice, and has seen them confused with pulmonary tuberculosis or miscalled pulmonary tuberculosis, with the exception of the four entities followed by a minus sign in parentheses. Authenticated cases are available, in the literature, in which these four also were the source of erroneous roentgen diagnoses of tuberculosis.

## Diseases, Disorders and Anomalies Which May Resemble Pulmonary Tuberculosis in the Roentgenogram

### A. *Anatomic Variations*

1. Broad vascular markings
2. Anomalous fissures and veins
3. Sternocleidomastoid tendon

\* Presented, by invitation, before the annual meeting of the American College of Physicians, San Francisco, April 19-23, 1948.

4. Rib cartilage calcifications
5. Rib anomalies
6. Muscle, etc. folds (e.g. following mastectomy)
7. Bronchial and vascular anomalies
8. Bronchial cartilage calcifications

*B. Shadows of Extrinsic Origin Including Artefacts*

9. Coils of hair over lung apex
10. Clothing
11. Medication on skin
12. Cutaneous lesions (warts, etc.)
13. Subcutaneous nodules (fibromata, foreign material, etc.)
14. Tumors of the thoracic wall
15. Enlarged or calcified nodes (lower neck, axillae, etc.)
16. Screen defects
17. Processing defects (especially undeveloped areas)
18. Rib irregularities (excess callus, surgery, etc.)

*C. Diseases of Lymphatics*

19. Adenopathy, non specific (hilar, etc.)
20. Lymphangitis, non specific
21. Hodgkin's disease
22. Lymphosarcoma
23. Leukemia
24. Carcinoma, metastatic (lymphatic spread)
25. Sarcoidosis (Boeck)
26. Silicosis
27. Silicatosis, etc.?

*D. Diseases and Disorders of Blood Vessels*

28. Venous dilatation (passive congestion)
29. Arterial dilatation (especially congenital cardiovascular lesions)
30. Arteriosclerosis (pulmonary arteries)
31. Infarcts
32. Visceral angiitis (periarteritis nodosum)
33. Edema, lobar
34. Edema, lobular
35. Arteriovenous fistula
36. Pulmonary phleboliths (—)

*E. Bronchial Disorders*

37. Bronchial filling (blood, fluid, etc.)
38. Bronchial stenosis, mechanical (extrinsic)
39. Bronchial stenosis (inflammatory)
40. Bronchial stenosis, neoplastic (benign)
41. Bronchial stenosis, neoplastic (malignant)
42. Bronchial occlusion, intrinsic (foreign body, mucus plug, etc.)
43. Bronchiectasis
44. Cystic disease
45. Disc atelectasis

*F. Parenchymal Lesions Inflammatory (Infiltration or Consolidation)*

46. Bronchopneumonia
47. Lobar pneumonia (especially developing or resolving)
48. Pneumonitis unclassified
49. Pneumonia, aspiration
50. Viral pneumonia
51. Eosinophilic "pneumonia" (pulmonary hives, L. H. G.)
52. Lipid pneumonitis
53. Coccidioidomycosis
54. Actinomycosis
55. Blastomycosis (—)
56. Streptothricosis
57. Histoplasmosis

- 58. Bagassosis (—)
- 59. Silicosis with infection
- 60. Asbestosis with infection
- 61. Paragonimiasis (endemic hemoptysis)
- 62. Unclassified tropical diseases
- 63. Miscellaneous unclassified infections (e.g. lupus erythematosus)

*Neoplastic*

- 64. Carcinoma primary
- 65. Carcinoma metastatic
- 66. Sarcoma primary
- 67. Sarcoma metastatic
- 68. Lymphoblastoma (infiltr.)
- 69. Benign tumor

*Miscellaneous*

- 70. Cystic disease
- 71. Fibrosis (e.g. post-radiation)
- 72. Calcification
- 73. Cavitation (e.g. silicotic, etc.)
- 74. Emphysema (esp. apical bullae, etc.)
- 75. Compression (e.g. paramediastinal, etc.)
- 76. Alveolar lipiodol residues
- 77. Intrapulmonary hemorrhage
- 78. Siderosis
- 79. Unclassified occupational disorders (beryllium, etc.)
- 80. Allergic disorders (?)
- 81. Eosinophilic granuloma (—)

*G. Pleural Lesions*

- 82. Edema
- 83. Effusion
- 84. Thickening
- 85. Calcification
- 86. Tumor

*H. Miscellaneous*

- 87. Polycythemia vera
- 88. Crushing injuries
- 89. "Blast" lung

## SUMMARY

A reference list of diseases, disorders and anomalies which may resemble pulmonary tuberculosis in the roentgenogram is presented.

# PROTEIN BALANCE STUDIES IN PATIENTS WITH LIVER DAMAGE. II. THE RÔLE OF LIPOTROPIC AGENTS\*

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DURING the decade 1932–1942 a considerable body of data accumulated, which completely revamped prior concepts of liver damage, in that nutritional factors assumed a rôle of increasing importance in pathogenesis, prophylaxis, and treatment. The experimental work which produced this revolution emanated from several groups of investigators.

Best, Hershey and Huntsman<sup>1</sup> in 1932 showed that choline would prevent fatty liver, and in 1935 Best and Huntsman<sup>2</sup> noted that casein acted in a similar fashion when administered to rats on a high fat diet. In 1937 Tucker and Eckstein<sup>3</sup> demonstrated that methionine was largely, if not entirely, responsible for the "lipotropic" (i.e., hepatic-fat-mobilizing) effect of casein.

In 1939 György and Goldblatt<sup>4</sup> reported the occurrence of hepatic necrosis in rats on "vitamin 'B' " deficient diets. Griffith and Wade,<sup>5</sup> the same year, found fatty livers and hemorrhagic kidneys in animals maintained on low choline diets, and suggested that the relative cystine-methionine content of the diet might modify the choline requirement.

This entire picture was brought into focus in 1941 by reports from four groups of investigators, working independently, that "cirrhosis" (necrosis) could be induced by a low protein, high fat diet, and that such necrosis could be decreased in severity or prevented by the addition of choline, betaine, methionine, or higher levels of casein. The investigators responsible were György, McCollum, Sebrell, Webster, and their respective coworkers.<sup>6, 7, 8, 9, 10</sup>

It was also noted by some of these investigators that cystine aggravated the damage produced by a low choline and/or low methionine intake.

Protection against liver damage referable to carbon tetrachloride,<sup>11</sup> yellow fever virus,<sup>12</sup> and ethylene dichloride<sup>13</sup> in experimental animals has been conferred by the administration of excess amounts of choline. Similar observations have been made in the case of methionine<sup>14, 15, 16, 17, 18</sup> although only in protein depleted animals.

\* This paper was presented in part at the annual meeting of the Western Society for Clinical Research, which met in San Francisco on November 8, 1947. Received for publication March 18, 1948.

This work has been performed under a grant from the Office of Naval Research. Acknowledgments are made to Dr. Cox, of the Mead-Johnson Company, for supplies of Amigen; to the Wyeth Company, for supplies of methionine, "Meonine"; to Anheuser-Busch, Inc., for supplies of yeast of high vitamin content; to the Eli Lilly Company, for supplies of alpha tocopherol.

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The above observations, together with a large body of related investigation in other laboratories, performed during this same period, raised a host of questions, foremost among which were:

1. What might be the relationship between the types of experimental liver injury described above, to clinical human liver damage, acute and chronic?

2. Through what channels did methionine and choline exert their protective effects; why did cystine at least under some circumstances, aggravate the experimental liver damage?

3. Would methionine and/or choline prove to have specific therapeutic value in clinical liver damage, over and above the therapeutic effectiveness of a high protein diet as originally advocated by Patek<sup>19, 20</sup> and amplified by Connor?<sup>21</sup>

The final answer to the identity between experimental nutritional deficiency liver injury and human "hepatitis" and "cirrhosis" is still to come. It is discussed elsewhere.<sup>22</sup> Certainly there is much evidence in favor of such identity or at least of marked similarity in the respective pathological pictures.

As to the channels through which methionine and choline produce their protective effects, there is agreement on only one point, and speculation and disagreement beyond that point. Essentially complete agreement exists in regard to the mechanism of the lipotropic effects of choline and methionine. Choline itself is an essential constituent of phospholipids. Phospholipids are apparently essential for the normal transport of fat from the liver to fat depots. Inadequacy of available choline, therefore, results in an increasing amount of liver fat, as originally demonstrated by Best and his coworkers<sup>2, 23, 24, 25</sup> and since that time confirmed and added to by many investigators. Methionine, in turn, can serve as a choline precursor by virtue of its labile methyl groups, as demonstrated by du Vigneaud<sup>26</sup> in 1941. Ethanolamine (derived from glycine) was shown by Stetten<sup>27</sup> in 1942 to serve as a non-methylated precursor of choline. The steps in this formation are shown in figure 1.

Considerable disagreement and confusion exist beyond this point, chiefly in regard to:

1. The rôle of other amino acids and "vitamins," fatty acids, inositol, lipocaic, etc.—much too extensive a subject to discuss here.

2. The question as to whether methionine, perhaps by virtue of its sulfur content, plays some specific protective rôle not related to its function as a methyl donator. This will be further discussed in this paper. The observations of Tucker and Eckstein<sup>3</sup> and of György and Goldblatt, previously noted,<sup>6, 10</sup> are in point.

The evaluation of methionine and/or choline in the treatment of acute and chronic liver disease in the human is the specific function of this report. Data already in the literature are not too conclusive, chiefly because of the lack of controlled objective criteria.

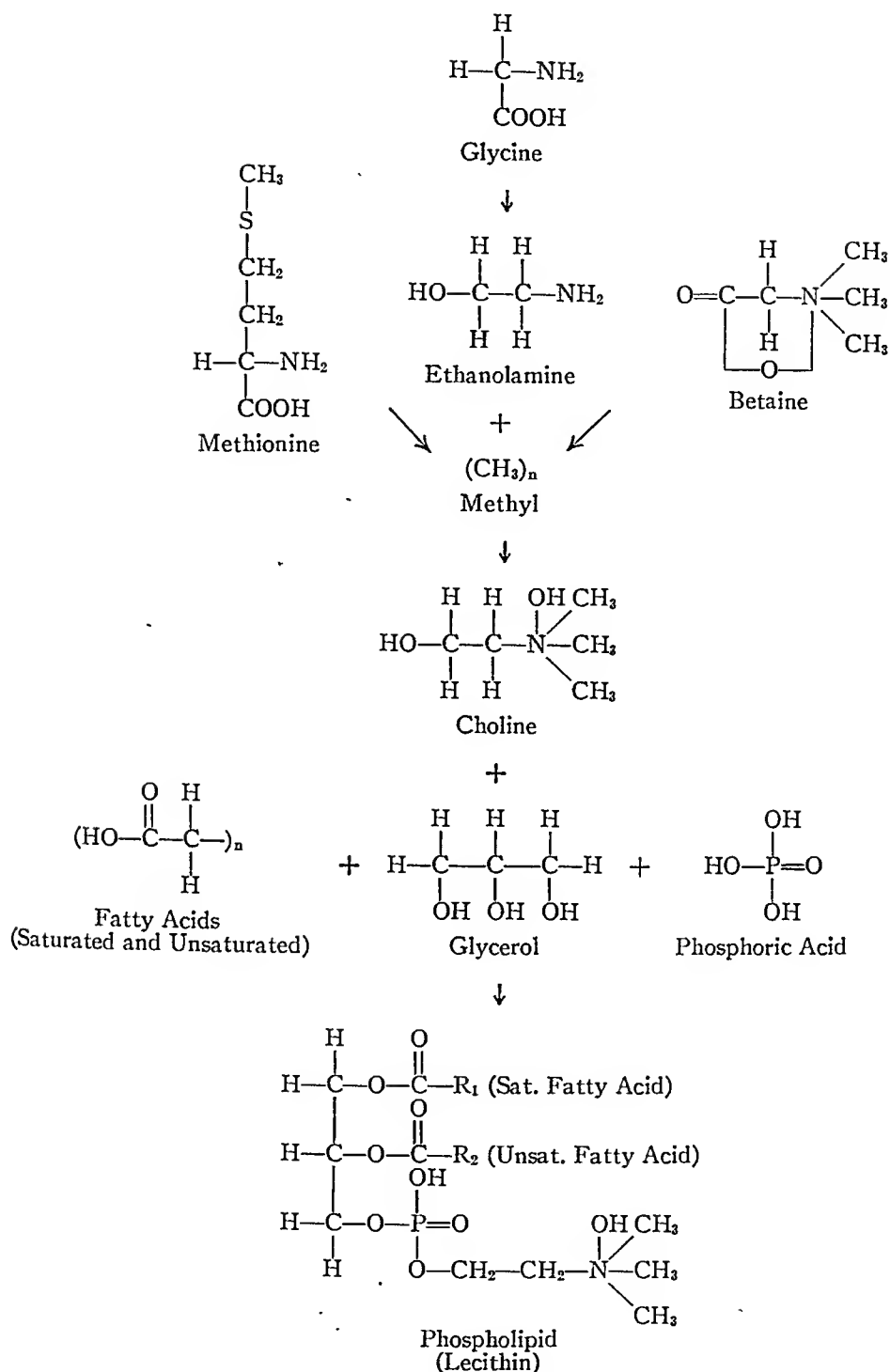


FIG. 1. Phospholipid formation. The rôle of choline and methionine.

Broun and Muether,<sup>28, 29</sup> Russakoff and Blumberg,<sup>30</sup> Beams,<sup>31</sup> and Morrison<sup>32</sup> have reported series of patients with chronic liver damage treated with choline and/or methionine, with or without a high protein intake, and are fairly unanimous in their belief that these agents are of some value.



Beattie and co-workers,<sup>33, 34</sup> Marshall,<sup>35</sup> Peters, et al.<sup>36</sup> and Eddy<sup>37, 38</sup> report the prophylactic and therapeutic use of methionine in individuals exposed to carbon tetrachloride and arsenic, and conclude that the evidence is in favor of a protective effect. Stewart and O'Brien<sup>39</sup> take issue with Professor Beattie's conclusions. Hartmann and Singer<sup>40</sup> report a case of arsenic poisoning in which they felt that methionine administration was without effect.

The use of methionine, choline and cystine in the treatment of patients with acute hepatitis has been the subject of a considerable body of reports.<sup>41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53</sup> The interpretation of results is varied but in most instances the data interpreted are insufficiently controlled. This is, of course, the weakness inherent in most clinical evaluation unless the effectiveness of a given therapeutic agent is unequivocal. The extreme degree of spontaneous variation in intensity and duration of infectious hepatitis makes for more than average difficulty in such evaluation. As will be noted presently, this same spontaneous variation has made the interpretation of some of our own data in patients with acute liver disease somewhat difficult.

It seemed to us, then, that the question as to whether choline and/or methionine, *over and above the amount present in a diet containing large amounts of protein and adequate quantities of other dietary constituents has a beneficial effect on patients with liver damage*, still remained to be answered.

It did not seem probable that further evaluation on the basis of clinical observation, or change in usual liver function tests would help to supply the necessary answer.

In the original paper in this series<sup>54</sup> it was postulated that because of insufficiency of normal protein anabolic and catabolic processes, patients with liver disease would tend to be in negative nitrogen balance, this despite the failure of Post and Patek<sup>55</sup> to demonstrate such a negative balance in such patients. Our findings for the most part confirmed those of Patek and Post; i.e., a consistently negative nitrogen balance was rarely found in patients with severe liver damage. Nonetheless, it seemed inescapable that such patients must have major qualitative disturbances in protein formation and if this were so, it seemed not improbable that the administration of methionine and/or choline might correct to some degree this qualitative defect, with the resultant production of a strongly positive nitrogen balance in response to the administration of these agents. The work presently to be discussed was designed to test this hypothesis.

Immediately after the beginning of this work, reports by Johnson et al.<sup>56</sup> and by Cox et al.<sup>57</sup> appeared simultaneously, indicating that methionine added to the diet of humans (without liver damage) did *not* affect the nitrogen balance, in contrast to the positive effects noted in rats and dogs by Allison, Anderson and Seeley<sup>58</sup> and by Brush, Willman and Swanson.<sup>59</sup> To the best of our knowledge, no similar human data are available in regard to choline.

In view of the greater protective effect of methionine as compared to choline in experimental animals as previously noted<sup>5, 6, 10</sup> and also as shown by Miller and Whipple in dogs,<sup>60</sup> we anticipated that if any effect were demonstrable methionine would have a greater effect than choline.

The work which follows presents the data accumulated in four patients with chronic liver damage ("cirrhosis"), one with "idiopathic hypoproteinemia," six with acute hepatitis, one with chronic hepatitis, and one with a mild hemolytic jaundice.

### METHODS

The diets employed, the procedures followed in patients studied during intravenous feeding, the analytical methods used are all presented in the first paper in this series.<sup>54</sup> Specific details will be described in the presentation of data on individual patients.

The balance charts follow the rules shown in the following diagram (figure 2).

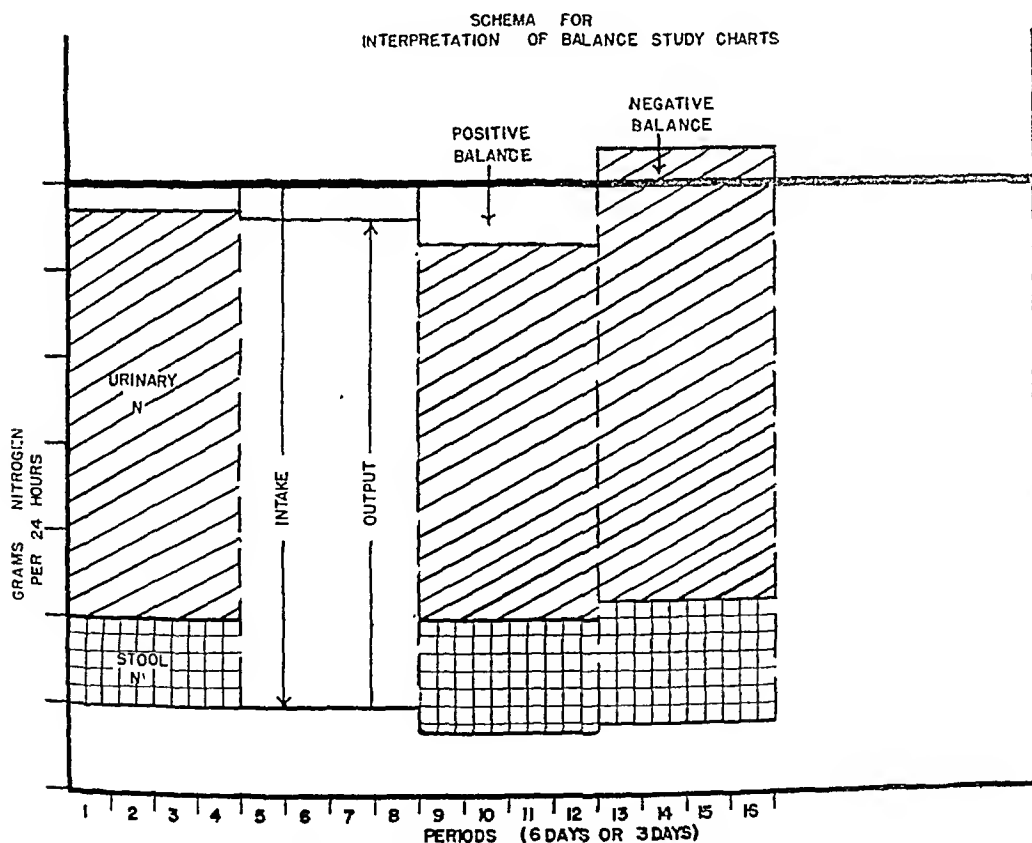


FIG. 2. Schema for interpretation of the balance charts.

### FINDINGS

#### CHRONIC LIVER DAMAGE:

*Two Long Term Oral Balance Studies.* The two men presented in this category both had a history of chronic alcoholism of more than 20 years'

duration; both were in the fourth decade; each had ascites on admission, which in the case of patient DAN had responded to dietary therapy prior to the beginning of this study; and which never responded to any therapy in patient DRE. The clinical, biopsy and liver function data on these men are presented in detail elsewhere.<sup>22</sup> Suffice it to say here that all liver function tests performed, including the A/G ratios, bromsulfalein-excretion, cephalin-flocculation, glycogen storage index, thymol turbidity, and serum bilirubin, were abnormal before, during, and after the balance study, and that clinically and histologically the findings in these men were in every sense of the word compatible with a diagnosis of advanced, active, chronic liver damage, referable to longstanding alcoholism, coupled with recurrent dietary insufficiency.

Both men were placed on the same balance diet, a three-day rotating, high protein, high vitamin (including supplemental vitamin K), high carbohydrate, moderately low fat, iso-caloric intake, as previously described, and had identical regimes up to the seventy-second day of the study, at which time patient DAN, because of domestic worries, became uncoöperative, with resultant undependability of his findings. Patient DRE continued for 96 days as originally planned.

All therapeutic periods were 12 days in length. Except for liver extract and alpha tocopherol, all medications and dietary supplements, once started, were continued throughout the entire period of study; i.e., the program was cumulative, up to the final 12-day post-treatment period (in DRE), at which time all medication was discontinued.

It will be noted that we purposefully used a diet which by any standard could be considered as thoroughly adequate, so that if any effect were obtained with any supplement, it could be considered as a specific effect.

The supplements added (figures 3 and 4) were in order:

Yeast, dried brewers' (Anheuser-Busch)—60 grams daily.

Choline chloride (by mouth)—9 grams daily.

Liver extract, crude (Eli Lilly & Company)—1 c.c. daily, I.M.

DL-methionine (Meonine, Wyeth, Inc.)—8 grams daily, by mouth, as 0.5 gram compressed tablets.

Alpha tocopherol (Eli Lilly & Co.)—300 mg. orally and then intramuscularly.

#### *Effects of Supplements in Patient DAN, Age 44 (figures 3 and 3a):*

##### *Yeast*

*Reason for giving:* Because of its high vitamin, high protein content.

*Effects:* Increased stool nitrogen. Decreased over-all nitrogen retention, with the production of a slightly negative as compared to a previously slightly positive balance. Clinical effects: none observable.

*Evaluation:* No significant effect.

# Choline

*Reason for giving:* For its "lipotropic" effect.

*Effects:* A marked decrease in excretion of urinary nitrogen, with the production of a strongly positive nitrogen balance—equivalent to

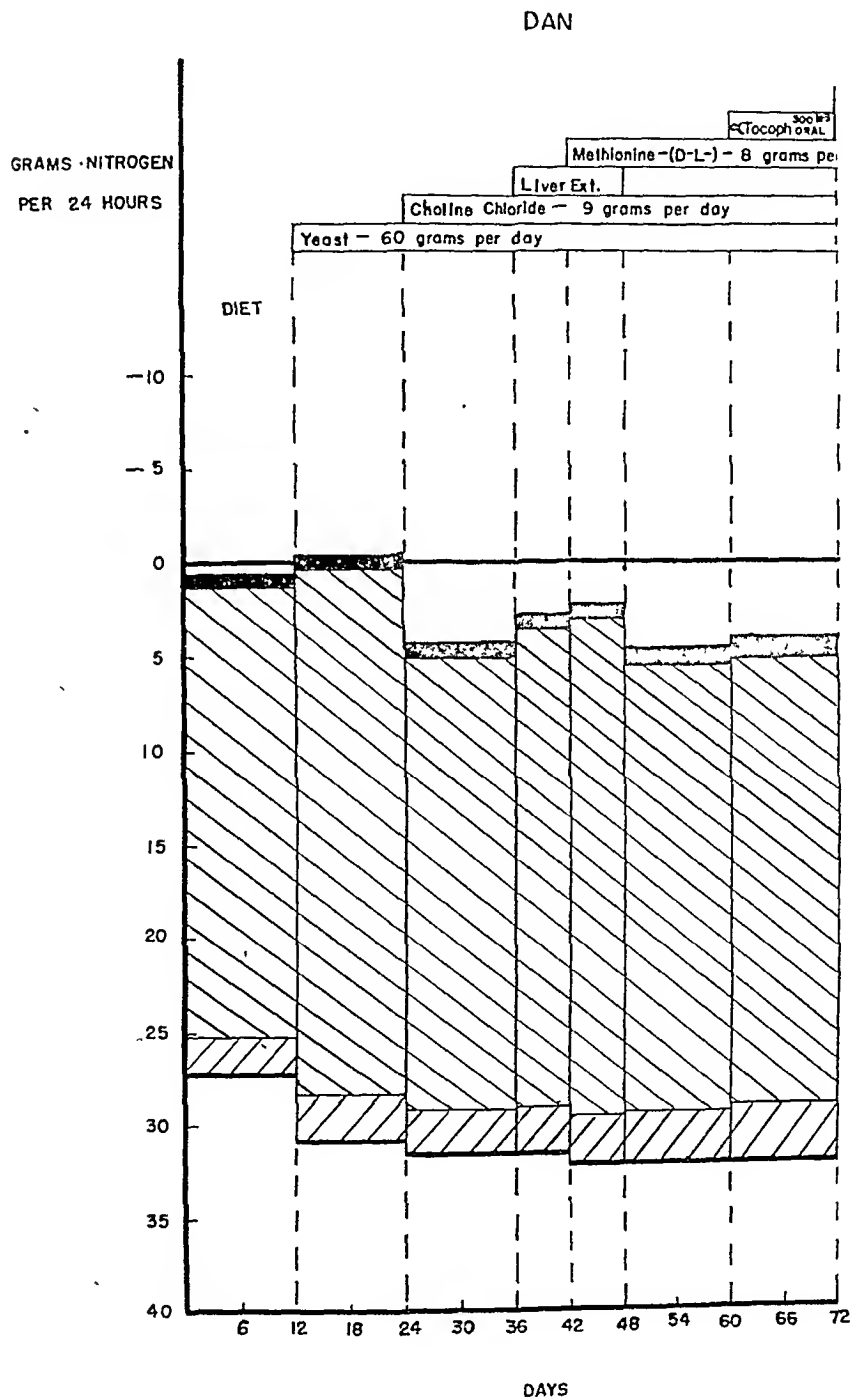


FIG. 3. Chronic liver damage. Effect of dietary supplements upon the nitrogen balance, patient DAN.

## DAN

Date	Period	Treatment (All medications cumulative except liver extract)	Daily			Balance
			Nitrogen Intake	Stool Nitrogen	Urine Nitrogen	
4/3/47 4/6/47 4/9/47 4/12/47	1	Diet	27.2 27.2 27.2 27.2	2.5 2.5 2.2 2.2	19.9 28.3 26.0 23.0	+ .40
4/15/47 4/18/47 4/21/47 4/24/47	2	Plus yeast	30.9 30.9 30.9 30.9	2.8 2.8 2.5 2.5	27.6 26.0 29.5 31.6	- .37
4/27/47 4/30/47 5/3/47 5/6/47	3	Plus choline	31.7 31.7 31.7 31.7	2.5 2.5 2.5 2.5	24.4 25.6 23.6 25.1	+4.52
5/9/47 5/12/47	3a	Plus liver extract	31.7 31.7	2.5 2.5	26.9 25.5	+3.00
5/15/47 5/18/47	3b	Plus methionine	32.0 32.0	2.8 2.8	26.6 27.3	+2.30
5/21/47 5/24/47 5/27/47 5/30/47	4	Stopped liver extract	32.0 32.0 32.0 32.0	2.5 2.5 3.0 3.0	25.6 27.6 22.6 22.8	+4.60
6/2/47 6/5/47 6/8/47 6/11/47	5	Alpha tocopherol 300 mg. oral	32.0 32.0 32.0 32.0	2.8 2.8 3.3 3.3	26.0 23.1 27.3 23.2	+4.05

FIG. 3a. Balance data on patient DAN.

about 30 grams of protein daily. Clinical effects: clinical improvement noted. Chemical effects: hepatic glycogen storage became less abnormal. Prothrombin time became less abnormal.

*Evaluation:* Protein anabolic effect unequivocal. Apparent clinical improvement.

#### Liver Extract

*Reason for giving:* Empirical.

*Effects:* Decreasingly positive nitrogen balance, which reverted to its previous level when liver extract was discontinued. Clinical effects—none noted, as compared to patient DRE (vide infra).

*Evaluation:* Unfavorable effect in terms of nitrogen balance.

#### Methionine

*Reason for giving:* For its lipotropic effect, and sulfur content (vide supra).

*Effects:* Nitrogen balance: no significantly greater effect than that already produced by choline. Clinical effects: continuing improvement.

*Evaluation:* No unequivocal evidence of any effect over and above that already initiated by choline.

*Alpha Tocopherol* (to be discussed elsewhere).

*Effects of Supplements in Patient DRE, Age 49 (figures 4 and 4a):*

It is to be emphasized that throughout the entire period of study, this man was constantly accumulating ascitic fluid. This presumably accounts for his positive balance, despite the progressive loss of body musculature which characterized him clinically, and which was only slightly retarded by the later administration of 100 gm. of serum albumin daily.

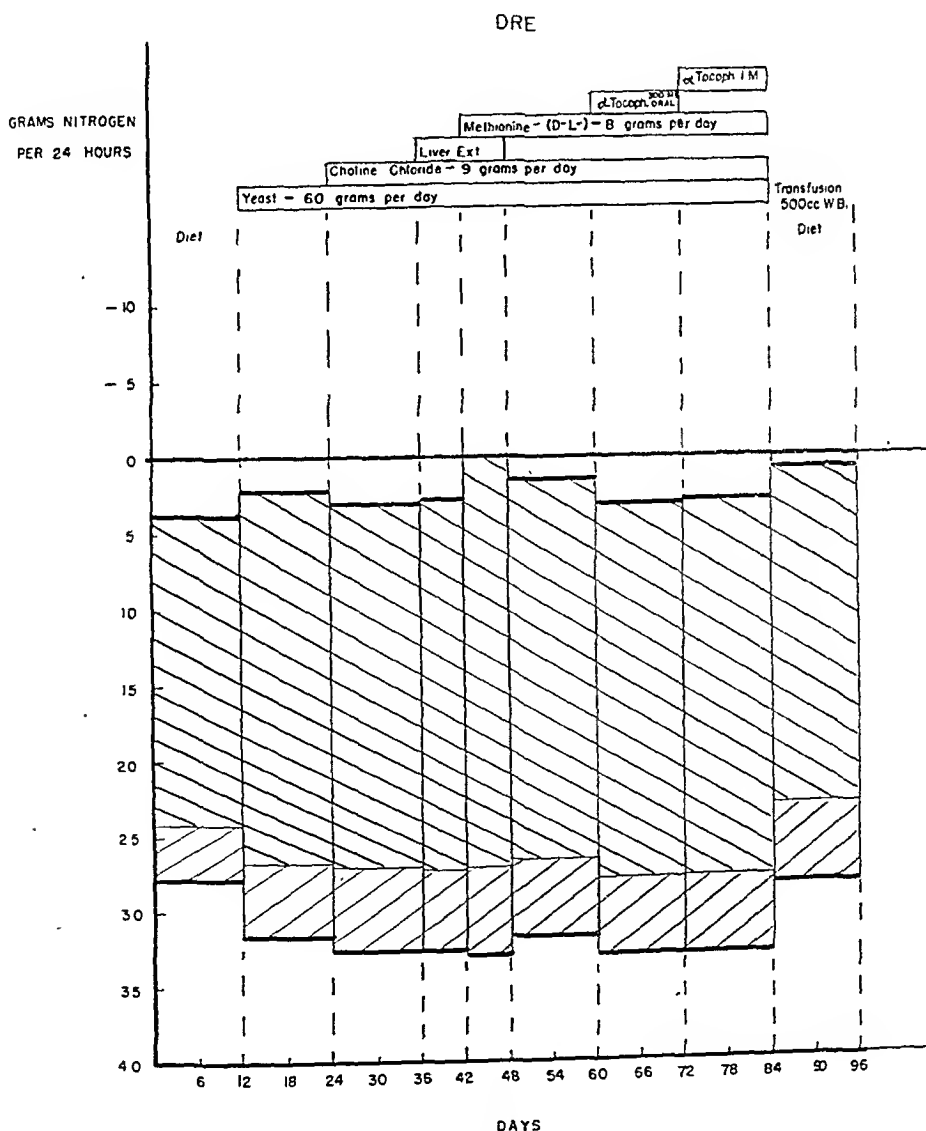


FIG. 4. Chronic liver damage. Effect of dietary supplements upon the nitrogen balance, patient DRE.

*Yeast*

Effects and evaluation as in DAN, only of greater magnitude. The stool nitrogen increased very markedly (32 per cent).

## DRE

Date	Period	Treatment (All medications cumulative except liver extract)	Daily			Balance
			Nitrogen Intake	Stool Nitrogen	Urine Nitrogen	
4/3/47 4/6/47 4/9/47 4/12/47	1	Diet ammonium chloride	28.0 28.0 28.0 28.0	4.3 4.3 3.3 3.3	20.5 19.5 19.5 20.5	+4.20
4/15/47 4/18/47 4/21/47 4/24/47	2	Plus yeast	31.7 31.7 31.7 31.7	4.5 4.5 5.5 5.5	24.1 24.0 24.3 26.5	+2.10
4/27/47 4/30/47 5/3/47 5/6/47	3	Plus choline	32.5 32.5 32.5 32.5	5.8 5.8 5.5 5.5	22.8 24.3 24.6 24.0	+2.92
5/9/47 5/12/47	3a	Plus liver extract	32.5 32.5	5.5 5.5	25.1 23.8	+2.55
5/15/47 5/18/47	3b	Plus methionine	32.8 32.8	5.8 5.8	28.0 26.3	-.20
5/21/47 5/24/47 5/27/47 5/30/47	4	Liver extract stopped	28.5 32.8 32.8 32.8	5.2 5.2 5.2 5.2	23.3 26.3 25.0 24.8	+1.67
6/2/47 6/5/47 6/8/47 6/11/47	5	Plus alpha tocopherol, 300 mg. oral	32.8 32.8 32.8 32.8	5.3 5.3 4.8 4.8	24.7 25.2 24.4 24.2	+3.12
6/14/47 6/17/47 6/20/47 6/23/47	6	Stopped alpha tocopherol. Began intramuscu- lar alpha tocoph.	32.8 32.8 32.8 32.8	5.2 5.2 5.3 5.3	24.3 25.5 25.3 24.6	+2.64
6/26/47 6/29/47 7/2/47 7/5/47	7	Whole blood Diet ammonium chloride	26.6 26.6 33.6 26.6	5.3 5.2 5.3 5.3	21.4 21.2 21.7 22.2	+1.47

FIG. 4a. Balance data on patient DRE.

*Choline*

*Effects:* No improvement in nitrogen balance over that noted in control period, presumably because of quantitative and qualitative insufficiency of liver tissue, i.e., inability to respond to stimulation.

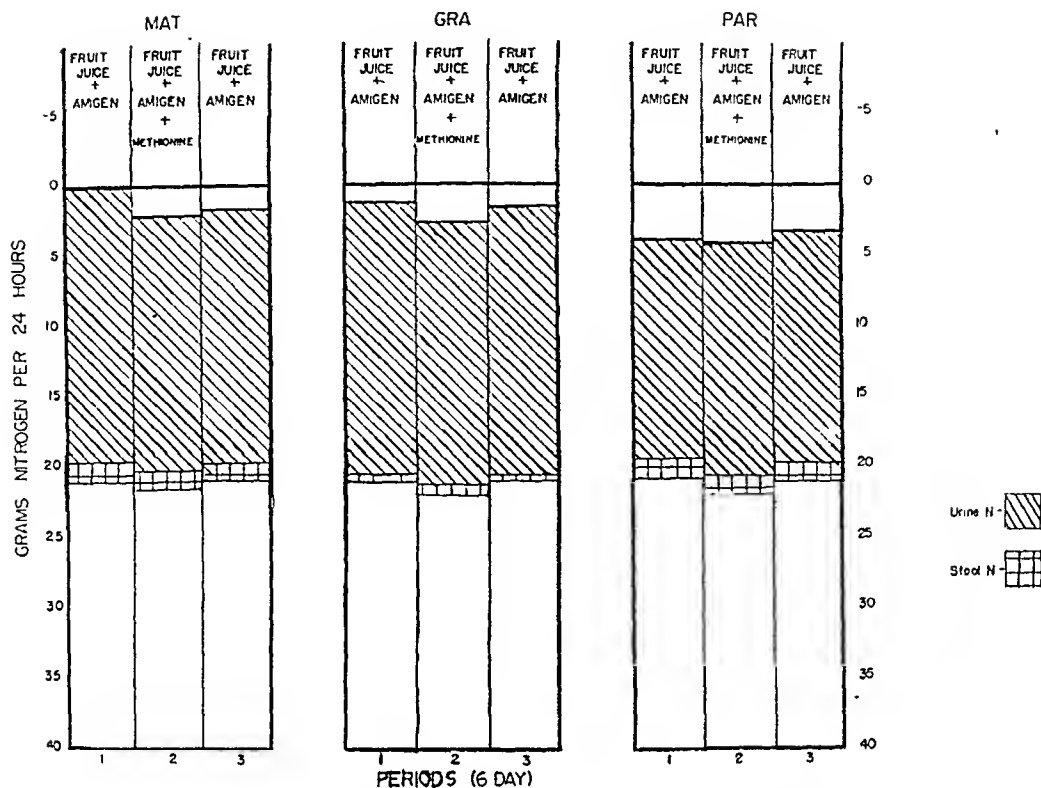


FIG. 5. Short term intravenous protein balance studies. Methionine effect. Patient MAT—idiopathic hypoproteinemia; patient GRA—chronic liver disease, active; patient PAR—chronic liver disease, active, convalescent.

### Liver Extract

*Effects:* Fluid retention appeared to be accelerated during this period; this increased retention disappeared when liver was discontinued. The nitrogen balance became progressively less positive.

*Evaluation:* Apparent unfavorable clinical and chemical effects. It was discontinued in both men because of the fluid retention in this patient.

### Methionine

*Effects:* Nitrogen balance essentially identical with that observed during the control period, i.e., no evidence of any effect. Except for possible slight decrease in the rate of formation of ascites, no clinical or chemical improvement was noted throughout the study.

### CHRONIC LIVER DAMAGE ET AL.:

#### Three Short Term Intravenous Studies (figure 5):

#### Description of Patients:

MAT, aged 40 (Described in detail elsewhere).

*Diagnosis:* Idiopathic hypoproteinemia, without demonstrable liver damage.



*Clinical and Laboratory Findings at Time of Study:* Anasarca, ascites, extreme hypoproteinemia, liver function tests normal, liver histology normal, moderate anemia, malnutrition.

*Diet (identical for all three men):* 3000 c.c. 5 per cent protein hydrolysate and 5 per cent glucose daily, by intravenous infusion. Sufficient fruit juice and vitamin supplements to make diet adequate calorically and dietetically.

*Methionine:* 9 gm. of the DL material daily, intravenously, as 3 per cent solution.

*Balance Study:*

*Pre-methionine (6 days):* Just in balance.

*On methionine (6 days):* Retention of 2.5 gm. daily.

*Off methionine (6 days):* Continued retention.

*Interpretation:* Positive methionine effect.

*GRA, age 48:*

*Diagnosis:* Chronic liver damage, with an acute exacerbation—ethanol-dietary origin.

*Clinical Status at Time of Study:* Clinical jaundice—decreasing. Palpable liver. Steady clinical and chemical improvement prior to study. No ascites.

*Balance Study:*

*Pre-methionine (6 days):* Retention of 1.3 gm./d.

*On methionine (6 days):* Retention of 2.9 gm./d.

*Off methionine (6 days):* Retention of 1.7 gm./d.

*Interpretation:* Significant methionine effect.

*PAR, age 49:*

*Diagnosis:* Chronic liver damage; active, regenerative—ethanol-dietary origin.

*Clinical Status at Time of Study:* Liver down 3 to 4 cm.; no jaundice; increasing energy; liver function tests becoming progressively less abnormal. Ascites had disappeared 3 to 4 months before this study.

*Balance Study:*

*Pre-methionine (6 days):* Strongly positive balance.

*On methionine:* Essentially unchanged.

*Off methionine:* Essentially unchanged.

*Interpretation:* Patient in strongly regenerative phase of chronic liver disease, not significantly influenced by extra-dietary methionine.

Both patients GRA and PAR had had large amounts of methionine by mouth up to two weeks before this study was performed. This may

have some bearing on the relative slightness of intravenous methionine effect on the nitrogen balance.

#### ACUTE AND SUBACUTE HEPATITIS; HEMOLYTIC SYNDROME:

Eight patients have been studied, six with acute viral hepatitis of varying severity; one with chronic hepatitis of fairly severe degree, and one with a low grade hemolytic jaundice (the latter for comparative purposes). The rapidly changing course of the disease, and the consequent shortness of the metabolic periods, makes the entire procedure less than desirable from the standpoint of interpretation.

All of these studies have been "intravenous" studies, the technics being

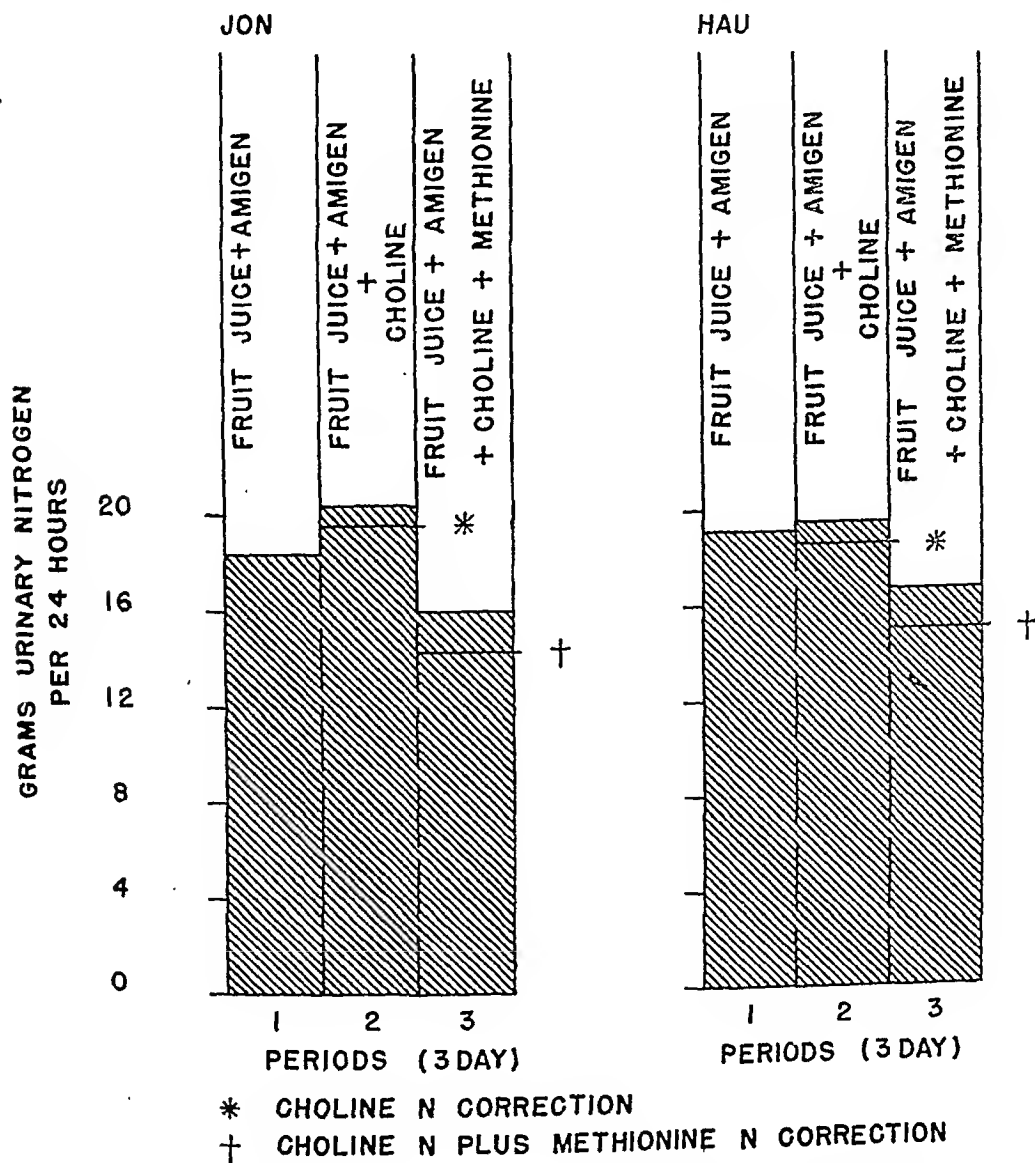


FIG. 6. Short term balance study in two patients with acute hepatitis.

essentially identical with those used in the preceding three patients, except that choline and methionine have been given by mouth instead of by vein.

*Patients JON and HAU, aged 24 and 32, respectively (figure 6):*

*Diagnosis:* Hepatitis, acute, severe. Duration 4 and 7 weeks respectively.

*Clinical Status at Time of Beginning Study:* Both patients were still severely jaundiced, with all liver function tests abnormal. Serum albumin—normal. Serum globulin—increased. During the nine days on the study, their liver function tests became progressively less abnormal.

*Balance Study:* Stool nitrogens were not done. Hence, only the urinary output is graphed. The intake was constant throughout, except for the added choline and methionine, and was essentially identical with that received by all other patients on the intravenous program.

Both men appeared to obtain no positive effect from choline, but a strongly positive (anabolic) effect from methionine. It would seem unlikely that a decrease in urinary nitrogen output of about 4 grams per day would be referable only to spontaneous clinical improvement, in the short period of time involved.

*Evaluation:* Probably a significant protein anabolic effect of methionine; apparently no choline effect (the increased nitrogen excretion on choline can be attributed to the increased nitrogen intake referable to choline per se).

*Patients BRO, BRU and CAS (figure 7):*

*BRO, age 19:*

*Diagnosis:* Hepatitis, acute, moderate severity; secondary lues. Duration (of jaundice), two weeks.

*Clinical Status:* Findings, those of classical acute hepatitis of somewhat more than average severity. All of the usual liver function tests were moderately abnormal. Progressive, slow improvement during period of study.

*Balance Study:*

*Diet Only (3 days):* Negative balance.

*Diet Plus Choline (3 days):* Strongly positive balance (net gain of 5 grams of nitrogen per day).

*Diet Plus Choline Plus Methionine (3 days):* Continued but not increased positive balance.

*Methionine Stopped (3 days):* Positive balance of same magnitude maintained in the second and third periods noted above.

*Interpretation:* Choline: significant anabolic effect. Methionine: no effect over and above that produced by choline.

*BRU, age 21:*

*Diagnosis:* Hemolytic state, of mild degree; idiopathic albuminuria.

*Clinical Findings:* Jaundice, mild, intermittently present for many years. Albuminuria without other evidence of renal damage. Red cell fragility—increased at times. Fecal urobilinogen—not increased. Liver function tests: slightly abnormal at times. Liver histology (biopsy): normal. Nutrition: excellent. Symptoms: none.

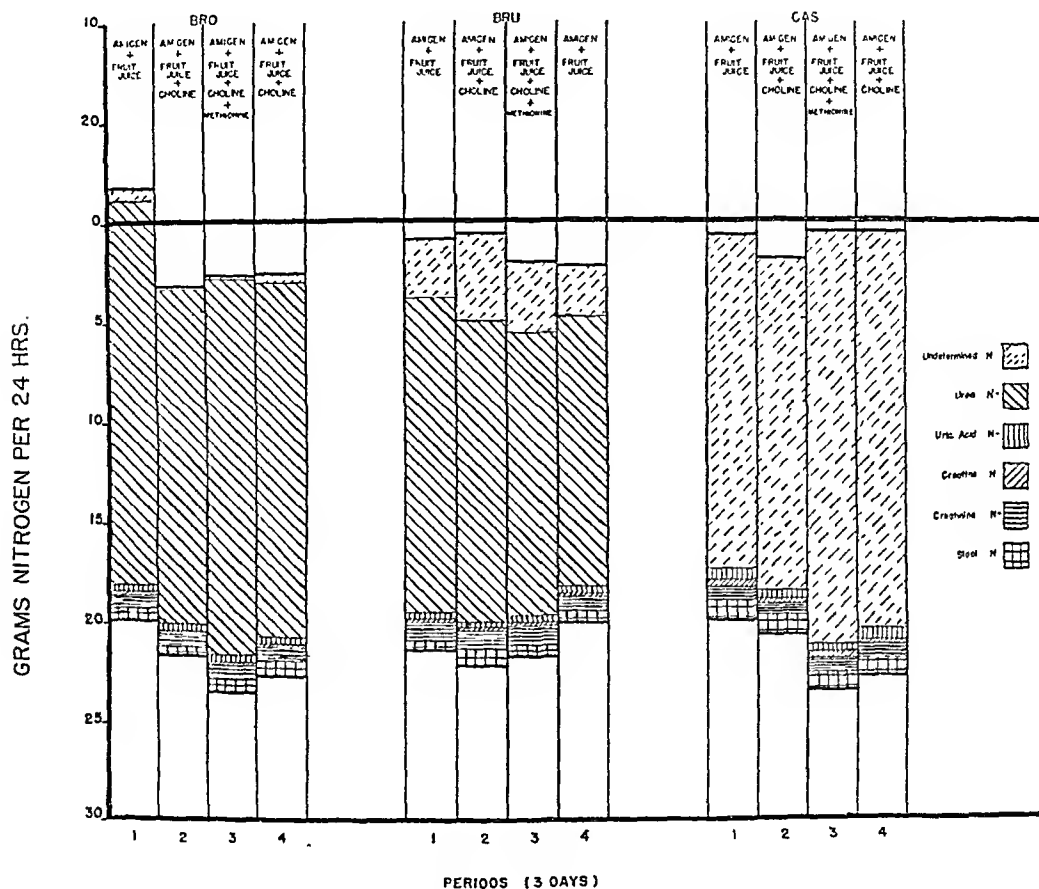


FIG. 7. Short term intravenous nitrogen balance studies. BRO—hepatitis, acute; BRU—jaundice, hemolytic, mild; CAS—hepatitis, acute. In patient CAS, urea was not determined, as such; i.e., "Undetermined N" in this patient includes urea N. The significance of the nitrogen partition is discussed elsewhere.<sup>54</sup> The large amount of "undetermined N" in BRU, at least in part, is referable to albuminuria. Dosage: Choline chloride, 9 gm. per day (oral); methionine (DL), 8 gm. per day (oral).

#### Balance Study:

*Diet Only (3 days):* Positive balance.

*Diet Plus Choline (3 days):* No effect.

*Diet Plus Choline Plus Methionine (3 days):* Strongly positive balance (net gain of about 2 grams daily).

*Diet Only (3 days):* Identical with the third period.

*Interpretation:* No choline effect; anabolic effect from methionine, maintained for some days after methionine was stopped.

CAS, age 24:

*Diagnosis:* Hepatitis, acute, moderately severe.

*Clinical Findings:* Essentially identical with patient BRO. Clinical improvement during study.

*Balance Study:*

*Diet Only (3 days):* Positive balance.

*Diet Plus Choline (3 days):* Net gain of 2 grams of nitrogen daily.

*Diet Plus Choline Plus Methionine (3 days):* Reversion to same excretion as that noted during the first period.

*Diet Plus Choline (3 days):* Identical with the third period.

*Interpretation:* None—unless one postulates that some limiting factor, perhaps a shortage of some other essential dietary constituent, operates, preventing more than a given amount of protein storage.

*Patients CUM, REY and WIL (figure 8):*

CUM, age 27:

*Diagnosis:* Hepatitis, chronic. Onset of acute hepatitis seven months previously.

*Clinical Findings:* Nutrition, fair; spider angiomas, many; liver enlargement, 4 cm.; splenomegaly, slight; hepatic fetor, definite; liver function tests, majority abnormal; liver histology, fibrosis and hepatocellular abnormality.

*Subsequent Progress:* Continuing evidence of an active, subacute hepatotoxic process.

*Balance Study:*

*Diet Only (3 days):* Strongly positive protein balance.

*Diet Plus Choline (3 days):* Significantly less positive balance.

*Diet Plus Choline Plus Methionine (3 days):* Balance identical with second period.

*Diet Plus Choline (3 days):* Slightly more positive balance.

*Interpretation:* In doubt. This man clinically fails to make an adequate response to any and all of the usually effective therapeutic agents. The paradoxical decrease in nitrogen retention with choline and methionine may be referable to the same obscure factors.

REY, age 25:

*Diagnosis:* Hepatitis, acute, moderate. Duration of 2½ weeks.

*Clinical Findings:* Typical for the disease. Decreasingly abnormal function tests during period of study.

*Balance Study:*

*Diet Only (3 days):* Strongly positive balance.

*Diet Plus Choline (3 days):* Identical with first period.

*Diet Plus Choline Plus Methionine:* Less positive balance.

*Diet Plus Choline:* Slightly less positive balance than in third period.

*Interpretation:* None. The concept of a lack of some other material, essential to protein anabolism might explain such observations.

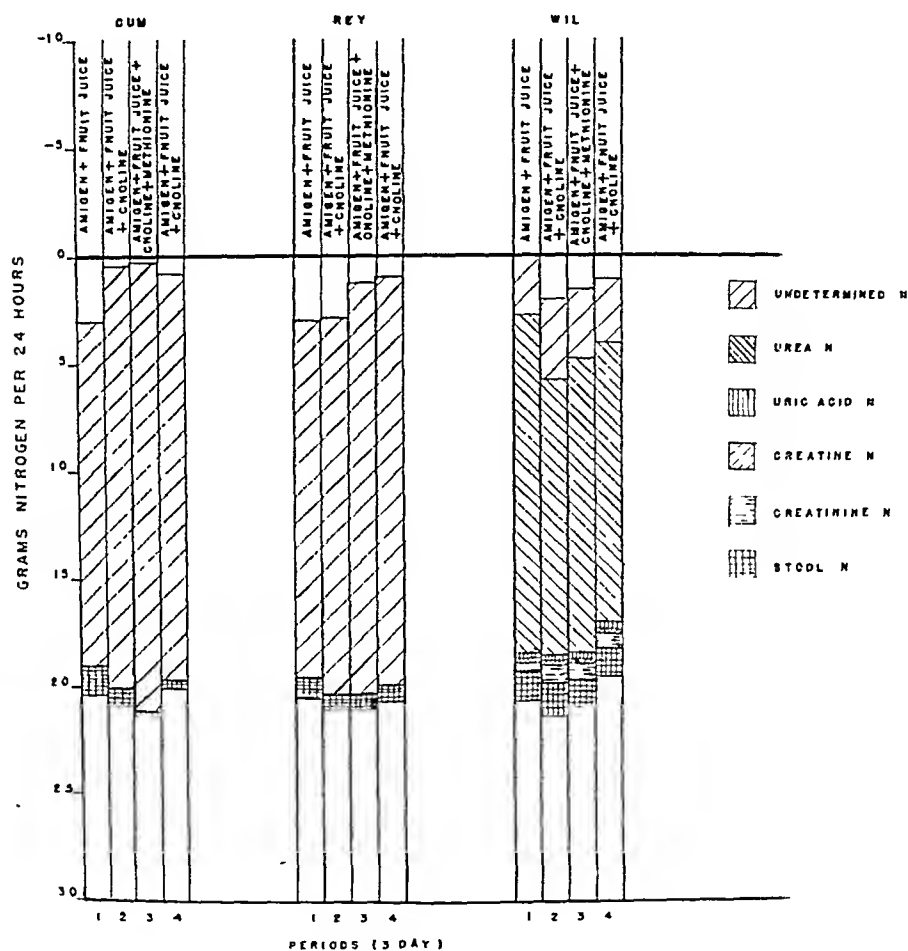


FIG. 8. Short term intravenous nitrogen balance studies. Patient CUM—chronic hepatitis, active; patient REY—hepatitis, acute, moderate; patient WIL—hepatitis, convalescent. Nitrogen partition data presented elsewhere. "Undetermined N" in CUM and REY includes *all* urinary N—i.e., partition not done. Dosage: Choline chloride, 9 gm. per day (oral); methionine (DL), 8 gm. per day (oral).

WIL, age 34:

*Diagnosis:* Hepatitis, convalescent. Onset 6 weeks previously.

*Clinical Findings:* No icterus remaining, slight hepatomegaly, symptom free. Most liver function tests still slightly positive.

*Balance Study:*

*Diet Only (3 days):* Just in balance.

*Diet Plus Choline (3 days):* Strongly positive balance.

*Diet Plus Choline Plus Methionine (3 days):* Less positive balance by about 1 gram of nitrogen daily.

*Diet Only (3 days):* Still less positive.

*Interpretation:* Anabolic effect of choline with a "wearing out effect" which is in no way inhibited by methionine. The hypothesis of the need for some additional, indispensable nutrient again arises.

## DISCUSSION

As stated earlier, the purpose of this work was to establish the effect or lack of effect of choline and/or methionine in terms of the production of a positive nitrogen balance, in patients with acute and chronic liver disease when these agents were added to diets high in protein and vitamin content, and adequate in calories. It is assumed that a protein anabolic effect may be regarded as a definitely beneficial effect.

Since the question had been raised but not settled, as to whether methionine acts only as a choline precursor in its relation to liver pathology, we purposefully have constructed all but three of our balance studies in such a manner as to bring out any "non-choline" effect of methionine if such existed.

We believe that we have obtained some satisfactory answers, and some stimulating but perplexing observations, the mechanisms of which at the present time are less than clear. The substance of these observations and interpretations, drawn from the preceding data, is as follows:

(1) *In chronic, active liver disease* choline will produce a profoundly positive effect upon the nitrogen balance, assuming that the dietary intake is adequate in other respects and that the patient has sufficient salvageable liver tissue remaining to permit of such effects.\* † This effect is perhaps related to some effect of choline other than simple mobilization of liver fat, inasmuch as patient DAN, whose data, of all patients included in this study, are most unequivocal, had no histological evidence of excess hepatic fat deposition during the period of this study.<sup>22</sup>

(2) *In chronic, active liver disease* we have no data which would suggest that methionine augments the protein anabolic effect of choline.

(3) *In chronic, active liver disease* methionine will apparently augment the protein anabolic processes initiated by an adequate diet, the protein of which is derived entirely from intravenous casein enzymatic hydrolysate (figure 5). That the effect was not more dramatic in these men, may be attributable to previous intensive methionine administration.

(4) *Patients with extreme protein depletion of non-hepatic origin* may

\*Since the completion of this study, patient DRE has died from progressive hepatic insufficiency, despite literally quarts of serum albumin; thus substantiating the concept of inability to respond positively to choline or any other stimulus in a manner identical with his running mate, DAN, because of previous extensive and irreversible liver damage.

† Further studies since the completion of this manuscript indicate that choline can produce an impressive anabolic effect in patients who have failed to manifest any anabolic response to methionine. It has also been shown that methionine in large dosage can be toxic to some individuals with severe liver damage.

obtain an anabolic effect from methionine (MAT, figure 5). This apparent contradiction to the findings of other workers<sup>56, 57</sup> may be referable to the cause of the protein depletion. Further study in this matter is progressing at the present time.

(5) In the evaluation of *patients with acute liver damage* (figures 6, 7, and 8) we feel on much less secure ground, chiefly because of the rapidly changing nature of the disease under study, itself a potentially major factor in the production of nitrogen balance changes; plus the attendant impossibility of obtaining experimental periods (control or treatment) of sufficient length to make unequivocal any data obtained.

Of the six acute hepatitis patients presented, three apparently obtained an anabolic effect from choline, three showed no effect. Two appeared to receive a positive effect from methionine as opposed to choline; one received no additional effect from methionine, as compared to choline alone, and three were actually in less positive balance with the addition of methionine than with choline alone, not an impressive array of data, all things considered.

(6) *One man with chronic, active hepatitis* (CUM, figure 8) appeared to receive an actual catabolic effect from choline and methionine—conceivably this observation as well as some similar observations on the acute patients might be explained by the same type of hypothesis as that devised to explain the “antilipotropic” effects of cysteine. Certainly this catabolic effect of a normally anabolic agent is no harder to explain than the failure of this man and many others like him to make a satisfactory clinical response to adequate rest, diet, and dietary supplements.

(7) Critical evaluation of the other dietary supplements—yeast, liver extract, alpha tocopherol—used in the course of the long term balance studies must await further work. It is perhaps permissible to speculate as to the significance of the increased urinary nitrogen in patients DAN and DRE (figures 3 and 4) during liver extract administration. But for the increased fluid retention in patient DRE, the increased nitrogen would probably not have been noted in time to stop the liver extract after a single 12 day period.

The late Dr. Hoagland and his coworkers have waxed rather enthusiastic over the beneficial effects of liver extract in cirrhotics<sup>61</sup> although their enthusiasm has been considerably tempered and diluted by time. It is not impossible that the beneficial effects which they observed may have been largely or entirely attributable to a high protein, high vitamin intake.

The observations of McHenry and Gavin<sup>62, 63</sup> regarding “biotin liver injury” may have some bearing on our findings. In any event, it may be well to put liver extract in the category of a possibly harmful agent in patients with liver damage, until further data are available.

(8) The probable significance of the huge amount of stool nitrogen in patient DRE together with a consideration of fluid balance changes and of the indications for different forms and avenues of administration of protein, are discussed in the first paper in this series.<sup>54</sup>



## SUMMARY

1. Choline and/or methionine over and above a high protein, high vitamin intake, have a protein anabolic effect in patients with chronic liver damage. This is probably another way of saying that they are potent therapeutic agents in some of these patients.

2. The effectiveness of these agents in patients with acute hepatitis is less clear cut. The intrinsic variability of the disease makes evaluation difficult, even under the controlled conditions of a balance study.

3. Our data do not establish any greater effect of methionine than of choline upon the protein balance. Since all patients received a high protein diet, it may be that the "choline effect" was actually a methionine sparing effect. The lack of fat in the biopsy sections would indicate some effect other than mere lipotropism.

4. Certain short term observations are reported in regard to the use of liver extract in patients with severe liver damage, which raise the question of deleterious rather than beneficial effects of this material.

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# A NEW TREATMENT FOR THE RELIEF OF OB- LITERATIVE DISEASES OF PERIPHERAL ARTERIES \*

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## INTRODUCTION

COMPLETE success in treating chronic obliterative peripheral arterial diseases depends upon stopping the progression of the pathological process and then developing a collateral circulation which will compensate for the arterial insufficiency. In thromboangiitis obliterans when smoking is stopped at least a recession of the superficial phlebitis can be expected, in a relatively short time. No specific measures are available in the management of arteriosclerosis. There are currently available many modes of therapy which have been devised with the hope of developing a competent collateral circulation. When improvement does follow their use it has taken so long that it is difficult not to credit time alone for the improvement. When vasodilator drugs are given intravenously or subcutaneously they usually fail in the lower extremities. The one exception is sympathectomy which, because of its immediate effect, has received wide acceptance. Its applicability, however, is limited in the arteriosclerotic group by the increased surgical risk commonly presented by older patients with cardiovascular arteriosclerosis and other degenerative diseases. That its immediate benefit will persist long enough to meet the future problems presented by a progression of the pathological process is questionable. It is apparent that a sympathectomy cannot be repeated several times if new indications arise. Grimson, in his review on the limitations of sympathectomy as a lasting measure, says that its immediate benefits fade with time due to the regeneration of the nerves and the sensitization of the muscles of the arteries.<sup>2</sup>

A procedure which can reproduce the immediate benefits of a sympathectomy and be repeated if new developments make it necessary, should be a most useful means of treating the obliterative peripheral arterial diseases. On the basis of recent preliminary studies in which radioactive sodium was utilized as a measure of changes in circulation it was found that the intra-arterial infusion of a dilute solution of histamine could approach this ideal.<sup>3</sup> We are now reporting its use in the femoral artery in patients with a severe insufficiency of the peripheral arterial circulation of their lower extremities caused by an endarteritis obliterans due to thromboangiitis or arteriosclerosis.

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## METHOD

*Technic of Histamine Infusion.* To overcome the pressure in the femoral artery the infusion bottle was prepared in the following manner. It was necessary to introduce the solution at a higher pressure than the diastolic pressure in the artery. The ordinary 500 c.c. infusion burette was capped by a stopper with two holes which was held down tightly with several strips of adhesive tape. Through one opening in the stopper, a piece of glass tubing was inserted reaching above the histamine solution. The outer end of this tube which contained an air filter was connected to two parts of the ordinary blood pressure apparatus by means of a Y tube. With the arm cuff rolled up snugly and held so with a stout elastic band, its rubber tubing was connected to one arm of the Y tube and the tubing of the manometer to the other. A closed circuit was thus established. When the bulb was inflated positive pressure was created in the inverted infusion bottle. This could be measured by the mercury manometer of the blood pressure apparatus.

With the skin and subcutaneous tissue anesthetized with procaine, a two inch, 20 gauge needle was introduced into the femoral artery.

To date well over 500 arterial punctures have been made and at no time have any local intra- or extraarterial complications resulted. An opportunity to examine the popliteal artery about two weeks after an intraarterial infusion of histamine occurred recently. The pathologist found no evidence of the recent puncture.

The bright red blood and its pulsating thrust into a Kaufman syringe attached to the needle were evidence of entry into the artery. The pressure was then raised or lowered until the pulsating blood could be seen only during each systole of the heart. The solution consisted of 500 c.c. of normal saline to which was added between 1.38 and 2.75 mg. of histamine acid phosphate (Lilly) equivalent respectively to 0.5 mg. and 1.0 mg. of histamine base. The infusion was given weekly and if the symptoms were totally disabling, biweekly. The dropping rate was measured in the drip indicator during the diastolic fall in pressure during which inflow into the artery took place. It was found that between two and five drops per heart beat permitted an erythema of the thigh to develop without any subjective symptoms. An asymptomatic flush of the face was found to be of little importance.

## MEASUREMENTS

The temperatures of the skin were determined with a Leeds Northrup potentiometer. The following method was employed. The local differences in the surface temperatures of the skin are noted and then corrected according to the spontaneous changes of the untreated leg. For example if there is a local rise of  $1^{\circ}$  C. on the treated foot and a drop of  $2^{\circ}$  C. on the control foot, the final change on the treated side is recorded as plus  $3^{\circ}$  C. It is time saving and obviates the necessity for temperature controlled rooms.

Oscillometric readings: Maximum amplitude of the pulsations of the

large vessels was recorded by a Boulitte oscillometer. These were made with the leg and patient in a horizontal position.

The diffusion of radiosodium was studied in many patients and these were recorded graphically.<sup>5</sup> Control measurements made before histamine infusions are termed basic curves. Unless otherwise stated when a graph was made to study the effect of a treatment or a procedure, the sodium was given between 10 and 20 minutes after the completion of the treatment. About 100 microcuries of  $\text{Na}_{24}$  in about 10 c.c. of water were introduced into the median basilic vein and a count of the radioactive emanation was made over the sole of the foot and the calf of the leg by placing these parts in contact with the window of a Geiger counter. It is our feeling when there is an increase in the diffusion rate of the radiosodium that it represents an increase in blood flow and total surface area of the minute vessels due to their dilatation and/or an increase in the permeability of the capillaries.

## RESULTS

The immediate objective responses to an intraarterial infusion of histamine are striking. The degree and extent of these reactions are obviously dependent upon the extent of the arterial block and the availability of a collateral circulation. The effects include a change in the color of the skin, its temperature, a distention of the superficial veins and alteration in the rate of diffusion of radioactive sodium. As the solution of histamine begins to enter the femoral artery a definite erythema spreads over the thigh from the groin and buttock to the knee becoming more intense as the treatment continues. The back of the leg, then the front and last, the foot, become pink. The extent of the spread is variable and patterns appear on the extremity in pink and white which suggest the location and degree of block in the larger vessels. The pale areas may become diffused later if the collaterals are dilated by the histamine. It is of interest to note that if the infusion is given too rapidly, thus permitting histamine to escape into the general circulation, erythema is observed to develop in the upper half of the body while the leg becomes only mottled and the foot even cyanotic. However, when the flow is slowed, permitting fixation of the histamine in the leg, then the skin of the leg and foot becomes pink and the rest of the body remains pale. Such an observation is corroborative evidence of the futility of giving vasodilators intravenously. Its generalized dispersal opens the more sensitive and healthy arteries of the upper half of the body first. Their dilatation diverts blood from the arteries of the lower half because total blood volume is essentially fixed in amount. When this occurs it is not only without value but it may actually be dangerous. This undesirable effect of misplaced vasodilatation has been observed after high sympathectomy when vasodilatation in the lower abdomen was so extensive that it diverted blood from the foot and precipitated gangrene. A rise in skin temperature follows the erythema rapidly in the thigh, more slowly in the foot. It is of interest to note

that the presence of erythema does not necessarily mean a rise in skin temperature. Many patients, however, do show a rise of 6° C. and some show none in the toes. A rise in the temperature of the skin over the calf of the leg is most significant. It indicates that blood flow to the calf muscles has been increased to a magnitude where it might be expected to relieve the pains experienced while walking and sleeping. The diffusion of radiosodium made after an infusion is accelerated indicating increased blood flow. This has been noted consistently over the calf muscles but not over the foot. This is to be expected because the block is more severe and collaterals are less numerous in the foot. The superficial veins invariably become distended even though the horizontal position is maintained. The oscillometric readings in the patients studied (table 1) were all very low as expected because none had palpable popliteal pulsations. Their amplitude never increased after single or multiple infusions of histamine. When a patient has a palpable pulse, the amplitude after a single infusion may rise as high

TABLE I  
Oscillometric Readings of Leg Treated with Arterial Infusion of Histamine

Patient	Upper Half	Lower Half
P. K.	2.0	1.0
B. D.	1.0	0.5
S. B.	1.0	0.7
L. P.	0.2	0.1
F. C.	1.0	1.0
O. R.	1.0	1.0
I. W.	0.5	0.1
W. K.	0.5	0.1
H. G.	0.5	0.1
R. S.	0.1	0.0
A. S.	0.1	0.0

as 25 per cent. These immediate and variable manifestations of vasodilatation after a single infusion will be later correlated with the cumulative effects of repeated infusions on walking and sleep tolerance reduced by obliterative disease.

No other treatment was used concurrently in the present study. Suggestion as a factor in improvement is ruled out by the fact that each patient had previously been subjected to one or more types of treatment from nine months to five years together with their attendant encouragement.

To evaluate the efficacy of histamine treatment we have chosen as criteria, benefit of two symptoms of arterial insufficiency in the lower extremities. The first is the number of blocks the patient is able to walk before he is forced to stop by pain in the calf of his leg. The second is sleep tolerance which represents the number of hours the patient can lie in bed in a horizontal position before he is awakened by pain in his calf muscles and forced to get out of bed for relief.

We have grouped all of our patients so that the effect of treatment on walking tolerance can be visualized in figure 1. The time interval between

treatments is not recorded but treatments were given weekly until the walking tolerance was increased to 10 blocks. Then one treatment a month was given until a tolerance of 18 to 20 blocks was attained when treatment ceased. If a recession occurred therapy was resumed until the desired level was again

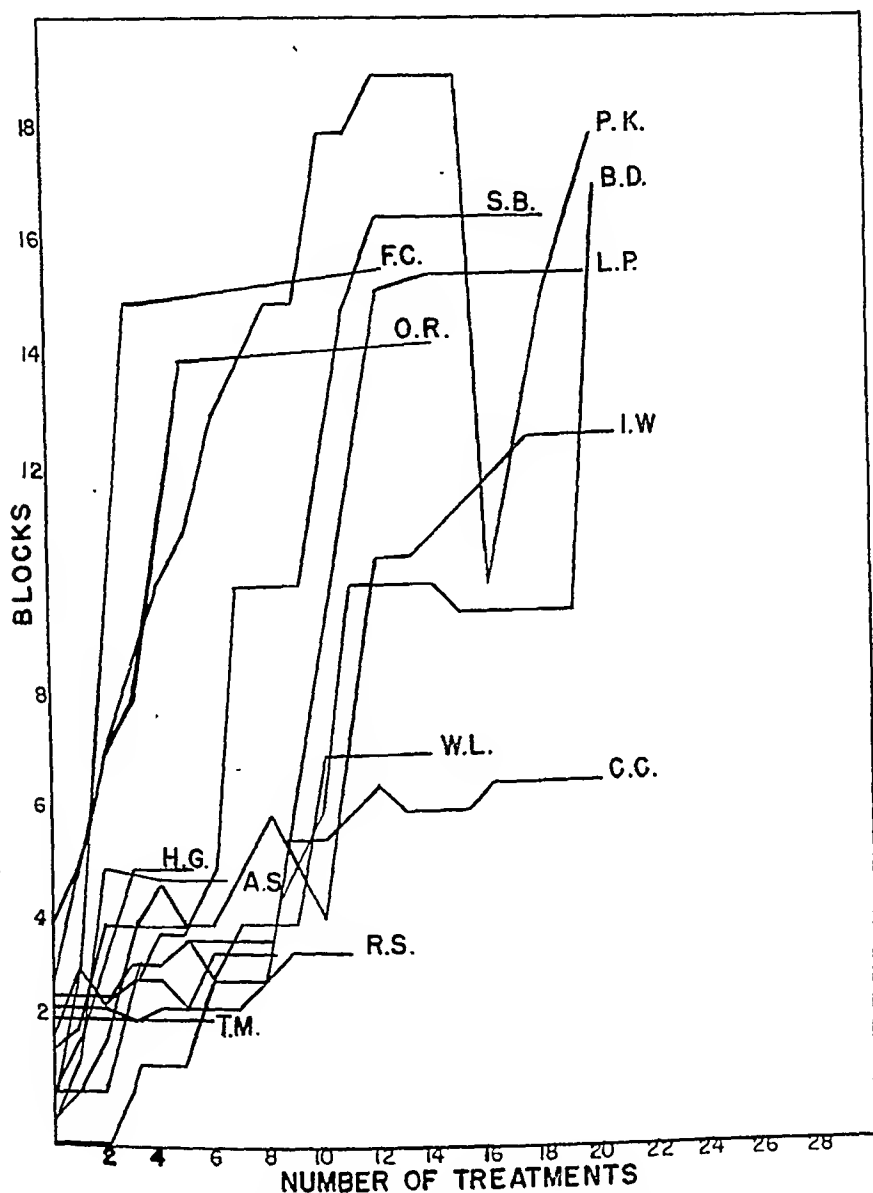


FIG. 1. The effect of repeated infusions of histamine into the femoral artery on decreased walking tolerance in obliterative peripheral arterial disease.

reached. Patients whose response to treatment was of this character were placed in the "very good" group. The response was considered to be only "good" when walking tolerance increased to between six and 10 blocks and reached a plateau. When this stage was reached the interval between treatments was also lengthened without permitting a relapse. The response was



called "poor" when no or negligible improvement was noted after six treatments. The effects on walking tolerance developed in response to histamine therapy as shown in figure 1, were as follows: "very good," 51 per cent;

TABLE II

The Effect of Repeated Infusions of Histamine into the Femoral Artery on Decreased Sleep Tolerance in Obliterative Peripheral Arterial Disease

Patient	Hours in Bed Without Pain Before Treatment	Number of Treatments Needed to Abolish Pain
L. P.	0	5
I. W.	2	2
C. C.	2	2
H. G.	1	4
W. K.	2	5
L. S.	4	3
H. S.	$\frac{1}{2}$ hr.	2
P. C.	4	2

"good," 33 per cent; and "poor," 16 per cent. The effect of treatment on sleep pain is recorded in table 2. Here we have had complete success and found patients most grateful. The improvement in walking and sleep tolerance has been prompt appearing after three to six weekly treatments.

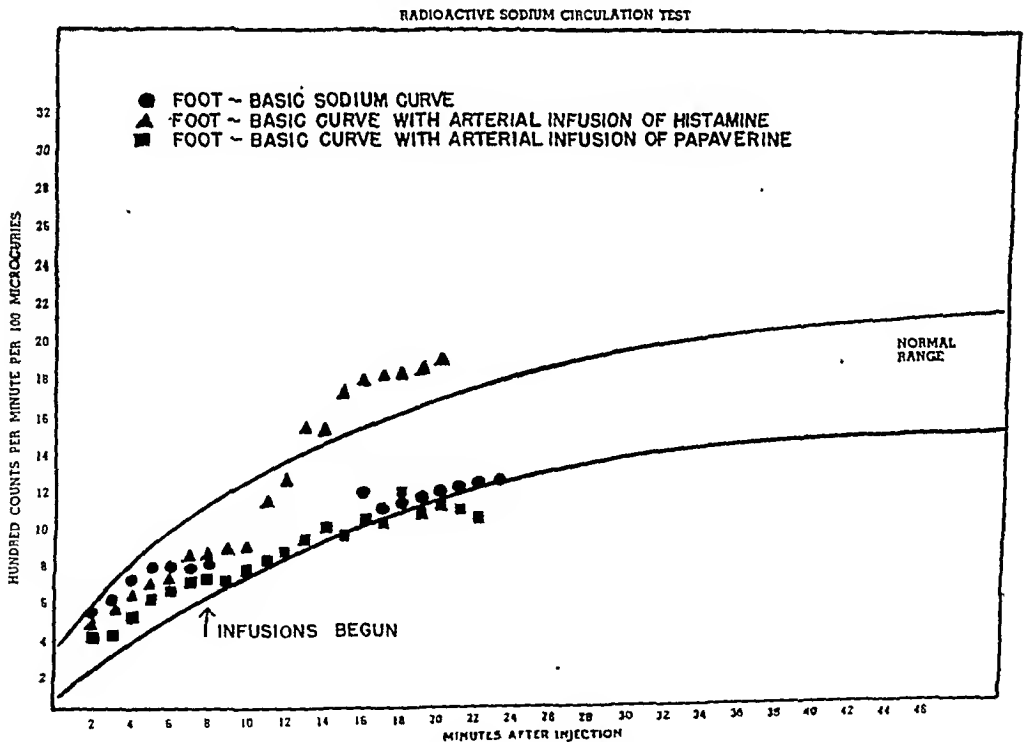


FIG. 2. Three radiosodium diffusion curves, one basic with no infusion, two made while normal saline was given by femoral artery for eight minutes when in one a solution of histamine (histamine base 0.35 mg. in 500 c.c. saline) and in the other a solution of papaverine HCl (90 mg. in 350 c.c. saline) was substituted. Histamine alone increased the Geiger count over the foot of patient I. W.

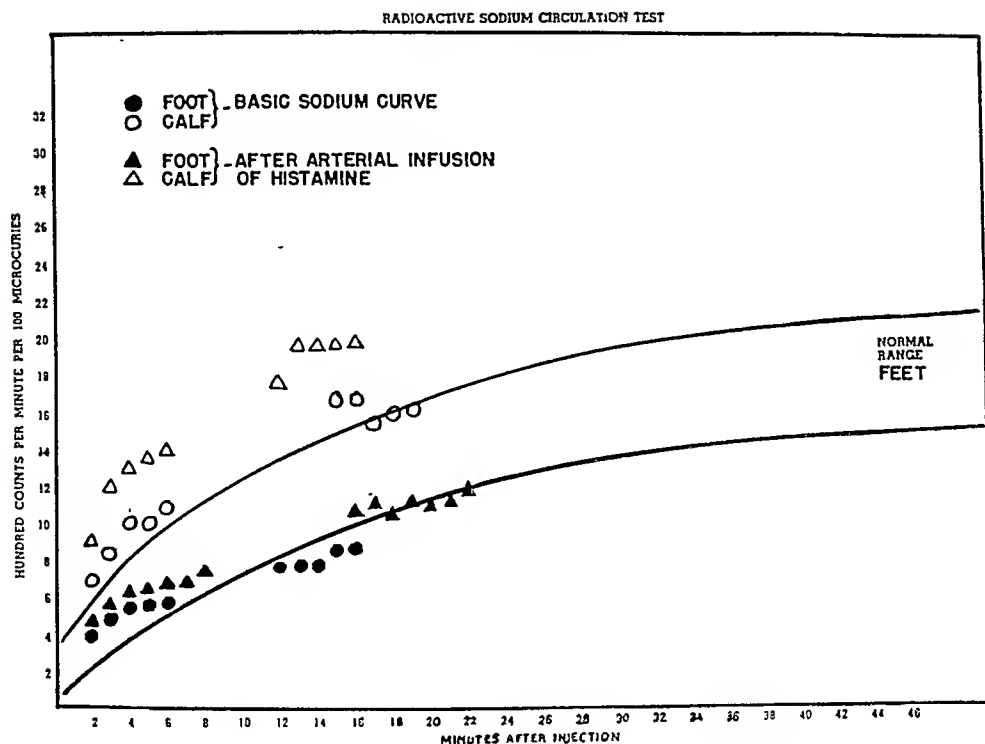


FIG. 3. The effect of an arterial infusion of 500 c.c. normal saline containing 0.5 mg. histamine base on the diffusion of radiosodium given intravenously. An increase in the Geiger count occurred over the calf but not over the foot of patient C. C.

These results produced by multiple infusions of histamine can be correlated with the immediate effects induced by a single infusion. It may establish patterns which could be used in estimating the amount and availability of the collateral circulation and the probability of its responding to this form of treatment. For this purpose a representative case history was chosen for each classification of response to therapy, namely, "very good," "good" and "poor."

Patient I. W. had a "very good" response to therapy. Her walking tolerance rose from one block to 15 blocks in 12 treatments and this improvement was maintained without any treatment for over five months. Before treatment the longest she could stay in bed was two hours and after one treatment her sleep was undisturbed. Her immediate response to a single infusion was just as dramatic (figure 2). The erythema reached down to her toes where the skin temperature rose  $6^{\circ}\text{C}$ . In this patient we found the greatest response in both the immediate and late effects. In contrast some of the patients in this group showed only a fair response to a single infusion. There was no rise in radiosodium diffusion in the foot but a rise in the calf. The increase in skin temperature was only  $2^{\circ}\text{C}$ . and the erythema did not reach the toes.

Patient C. C. exhibited a "good" response to therapy. After an infusion the erythema spread from the groin, down the back of his leg with an occasional blotch of pink on its anterior surface, while the foot remained white. Skin temperature rose on the back of the leg  $3^{\circ}\text{C}$ . and  $1^{\circ}\text{C}$ . on the dorsum of his foot and toes. The diffusion curve of radiosodium rose over the calf muscles but remained unchanged over

the plantar surface of his foot (figure 3). His objective response was not as good as that of patient I. W. and his subjective response to weekly treatments was not as good. It consisted of a rise in walking tolerance from one to seven blocks in 18 treatments and loss of sleep pain in three treatments. The foot, even though he continued working in a cold shed as an automobile repair man, became less numb and warmer. However, his walking tolerance has never risen higher and treatment must be continued to maintain this improvement.

Patient R. S. as representative of "poor" results received six treatments without any marked increase in his walking tolerance and it was discontinued. However, his pain was not as severe and he was able to return to work after having been disabled for many months. He reacted to a single infusion by developing an erythema of his thigh and leg but no rise in the surface temperature of his foot. In fact his first toe became slightly cyanotic. The radiosodium curve rose in his calf and foot (figure 4) and this was perhaps a portent for a good response to therapy. However, this did not materialize. He also had the lowest oscillometric readings of the entire group treated.

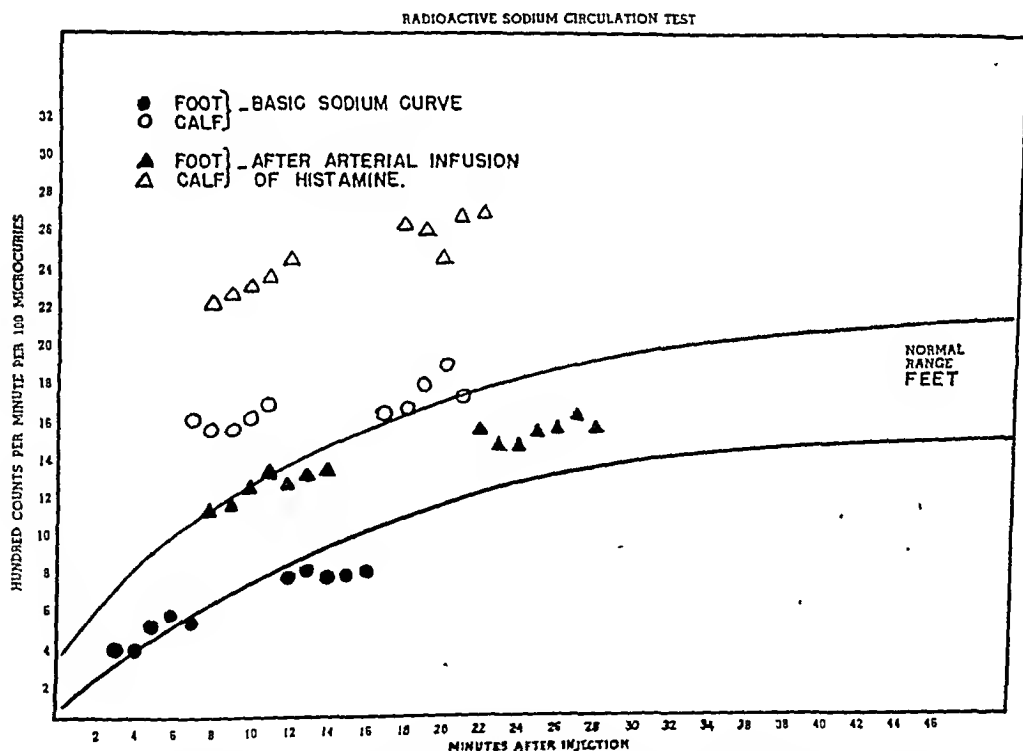


FIG. 4. The effect of an arterial infusion of 500 c.c. normal saline containing 0.5 mg. histamine base on the diffusion of radiosodium given intravenously. An increase in the Geiger count occurred over the foot and calf of patient R. S.

Two cases are recorded to further illustrate the difficulties in establishing the prognosis of therapy, when untoward extravascular events intervene to change the fate of an extremity.

Patient H. S. presented himself in the clinic with a walking tolerance of two blocks; a sleep tolerance of half an hour due to pain in the foot. Two lumbar blocks with procaine were performed but with no relief. They caused no rise in skin temperature and no distention of the veins. Two histamine infusions were then given a

week apart. These induced an erythema down to his toes but no rise in temperature, the superficial veins of the leg dilated, the radiosodium curve in the calf rose but remained unchanged in the foot. There was great clinical improvement, the patient was able to sleep and returned to work. A week later a man stepped on his toes while riding in a crowded subway train. The skin was broken and oozed. All his previous disability returned. Histamine infusions were again given but this time without lasting relief. Sympathetic blocks again gave no help. A bilateral sympathectomy of  $L_2$  and  $L_3$  was performed also without relief. A radiosodium diffusion curve three days after the first sympathectomy was lower than the basic curve made two weeks previously. Trauma, by causing an irrevocable vasospasm, introduced a new load on an already harassed collateral circulation.

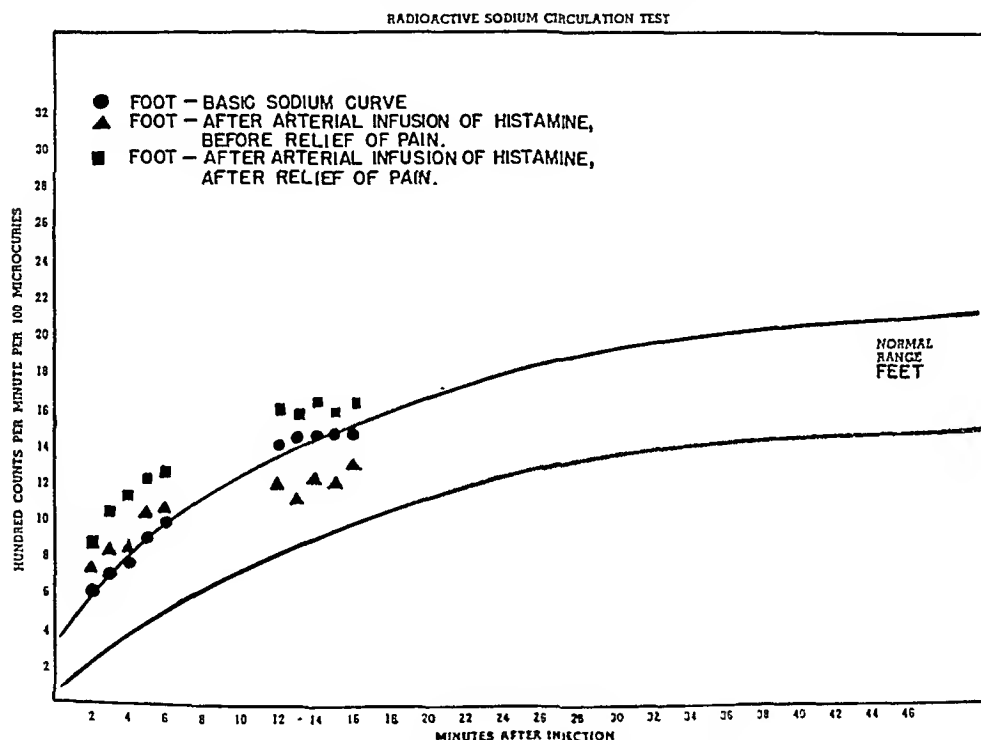


FIG. 5. Before pain due to an ingrown toe nail was relieved, an infusion of histamine induced a fall in radiosodium diffusion over the foot while after the relief of this pain the histamine infusion caused an increase in diffusion.

This is again illustrated by patient T. M. who was referred because of pain in his foot, limited walking tolerance and sleepless nights. Two infusions of histamine failed to cause a rise in radiosodium diffusion over his foot. An ingrown toe nail, partially embedded in the underlying skin, was clipped. The pain in the foot was now relieved. The next infusion of histamine was followed by a moderate rise in radiosodium diffusion. Figure 5 records the effect of pain on the radiosodium diffusion in the foot of this patient.

## DISCUSSION

It has been shown that histamine given by arterial infusion is a powerful dilator of all the components of the peripheral vascular system. Its increase of the temperature of the skin and radiosodium diffusion indicates that the arteries, large and small, are widened. The erythema and rubor of the skin

which follow its use mean that the precapillary sphincters are relaxed and the minute vessels are wide open. The superficial veins become visibly dilated. These physiological responses are probably as short lived as six hours, still as the results show cumulative and mounting improvement follows weekly infusion. Therefore it is reasonable to inquire why should such an enduring and competent circulation develop after histamine. An analysis of the problem in full perspective may yield the answer. To begin with, in each patient a primary influence such as smoking or a degenerative process initiates a block in one or more arteries. The arterial collaterals, though available, do not take over the burden because they are thrown into reflex spasm as a result of the original block and its attendant distress. In some, they open spontaneously in six weeks. In the group of patients treated with histamine this had not occurred when first seen.

From the benefit in walking and sleep tolerance obtained by about 85 per cent of them, it is apparent that their arterial blood flow is now effective and competent. In theory there are two ways in which histamine could bring this about. First, it could come about in the manner shown by Clark and Clark<sup>1</sup> in their experiment on the rabbit. They showed that under acute stimuli arterio-venous anastomoses developed from thread-like capillaries to five times their original size. Evidence for such violent vasodilating properties was presented in the results which follow a single histamine infusion. Their repetition should be able to develop arteriovenous anastomoses in great numbers. The second reason may be found in evidence which shows that the reversal of vasospasm following histamine will persist when there is no reflex extravascular cause for vasospasm. Pain can render histamine or a sympathectomy inert as a vasodilator permitting at most only temporary effectiveness. The clinical reports on patients H. S. and T. M. in the results are the basis for this impression. The walking and sleep tolerance of H. S. increased and his radiosodium diffusion in the calf rose after histamine but when his toe was accidentally crushed, then histamine and later a lumbar sympathectomy failed to help him. The latter was followed three days later by a drop in radiosodium diffusion. Similarly T. M. first showed a drop in radiosodium diffusion indicating no vasodilatation following a histamine infusion. After his pain due to an infection and an ingrown toe nail was relieved, the same type of infusion was able to bring about a rise in radiosodium diffusion (figure 5).

Fear has also been shown to be a cause of vasospasm.<sup>4</sup> A recent experience gave visual confirmation of this phenomenon. A marked rubor was developing during an infusion of histamine into the femoral artery of a patient with scleroderma when it suddenly faded completely from her foot after the patient began discussing the details of the death of a close relative. In less than two minutes after the conversation was terminated, with the arterial infusion still running, the pallor was replaced by a bright erythema. Dread fear had again completely reversed the dilatation caused by histamine. It follows then that the crux of the success of histamine therapy rests not

alone on the presence and availability of a collateral circulation which it can activate but also on the absence of a continuing cause for a reflex and histamine resistant vasospasm of these same collaterals. The patterns established in response to a single arterial infusion of histamine are not, as the results show, sharply delineated for each classification of response to therapy. However, when these are correlated with all the variables, vascular and extravascular, it is possible to grade the extent of the occlusion and the probability of circumventing it with histamine given by artery.

### CONCLUSION

1. A new treatment for the relief of obliterative arterial disease has been described.

2. When a dilute solution of histamine is repeatedly given by intraarterial infusion, relief is obtained by the patients who are incapacitated by a limitation in walking and sleep tolerance.

3. Our results show that walking tolerance was raised to normal in about 85 per cent of the patients treated and the pain present during sleep was abolished in all.

4. From the correlation of effects produced by a single intraarterial infusion of histamine on the color and temperature of the skin and the radio-sodium diffusion curves of the foot and calf with the final results of treatment, we are decided that it is only by equating the degree of arterial block as shown by these observations with the presence or absence of extravascular causes for spasm that one will be able to prognosticate with some degree of accuracy the outcome and fate of the limb after treatment with histamine.

The author wishes to express his gratitude to Professor Edith H. Quimby and her assistant, Miss Charlotte Schmidt of the Department of Radiological Research, for making the radioactive isotope studies possible.

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# CASE REPORTS

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## THE USE OF TETRAETHYLAMMONIUM BROMIDE AS A DIAGNOSTIC TEST FOR PHEOCHROMOCYTOMA \*

By JOHN S. LADUE, M.D., Ph.D., F.A.C.P., PAUL J. MURISON, M.D., and  
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### INTRODUCTION

THE purpose of this case report is to present and compare the reactions of a patient with a medullary tumor of the adrenal gland (pheochromocytoma) to the intravenous administration of histamine phosphate and of tetraethylammonium bromide.

Roth and Kvale<sup>1</sup> found that three patients with pheochromocytoma who were given 1/40 to 1/20 of a milligram of histamine phosphate intravenously responded with a rise of 100 mm. of Hg or more in the blood pressure reading. Patients who had essential hypertension or hypertension secondary to renal disease and those who were controls or hyper-reactors to the cold pressor test evidenced a slight fall or rise or no change in the blood pressure. Hence, a marked rise in blood pressure after the injection of histamine phosphate has been proposed as a confirmatory test for the presence of a pheochromocytoma.

### CASE REPORT

R. S., a 41 year old salesman, had been comparatively well, except for insomnia, nervousness, and bilateral tinnitus of five years' duration, until June, 1945, when he began to have what he called heart attacks. These were characterized by the sudden onset of a nervousness which he described as "a pounding of my heart with the blood rushing to my head," soon followed by sweating, by severe, pounding, generalized headaches, and by terrific abdominal pain, "as if someone had struck me in the solar plexus with his fist." These episodes usually occurred during the day, lasted 10 to 15 minutes, and were not relieved by self-medication, hot packs, or other similar measures. The patient was totally incapacitated during a seizure, being doubled up with pain, unable to suppress moans, and drenched with cold sweat. When the symptoms had subsided he was left completely exhausted for an hour or more. The attacks increased in frequency and severity so that the patient was loath to leave his quarters. Eventually, he noticed that attacks seemed to be precipitated by his lying in bed propped on his left elbow or by a sudden twisting of his body to the left, although his symptoms occasionally appeared while he was lying on his right side. He tired easily and was forced to give up tennis and other strenuous activity. Almost coincidentally with the first of his attacks, he noticed a marked loss of libido.

The patient consulted several physicians and was told that he had high blood pressure. Sedatives were prescribed, and he was advised to avoid nervous tension

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From The Pack Medical Group, New York, N. Y.

and strenuous exertion. His social background included an unstable childhood environment, an unhappy marriage, and recent unemployment, and this history strengthened the impression that all his complaints might be psychosomatic in origin.

When the patient first presented himself at our offices on July 3, 1946, a little more than a year after his first attack, physical examination revealed a well developed, muscular, well nourished, white male who appeared to be in an excellent state of general health. Except for blood pressure readings varying between 150 and 180 mm. Hg systolic and 100 and 120 mm. diastolic, the physical findings were all within normal limits. Carotid sinus pressure resulted only in a slowing of the heart rate from 90 to 85.

The abdomen was soft and non-tender, and no masses were palpable, although the lower pole of the right kidney was felt. The extremities were symmetrical, and the reflexes were physiological. Mild arteriovenous nicking was noted in the eye grounds.

Routine hematological studies and urine analyses revealed nothing except a trace of albuminuria. The urine concentration test gave a specific gravity of 1.028, and the urea nitrogen was 27.5 mg. per 100 c.c. of blood. Phenolsulfonephthalein excretion was 15 per cent in one-half hour, 25 per cent in one hour, and 5 per cent in the second hour, a total excretion of 30 per cent, on September 11, 1946. By September 16, 1946, the phenolsulfonephthalein excretion had risen to 45 per cent in one-half hour and 60 per cent in one hour, with a total two hour excretion of 60 per cent. The urea nitrogen had fallen to 18.4 mg., and the total protein was 6.10 gm., with 4.30 gm. of albumin and 1.80 gm. of globulin. The blood cholesterol was 441 mg., and the blood sugar 134 mg. per 100 c.c. of blood. Wassermann and Kahn reactions were negative.

An intravenous pyelogram showed that the right kidney was flattened at its superior pole and displaced downward by a soft tissue mass (figure 1). A roentgenogram of the chest was within normal limits; the electrocardiogram showed slight left axis deviation with one millimeter elevation of  $ST_1$  and a one millimeter depression of  $ST_2$  and 3.

On the patient's second office visit, he was asked to try to produce an attack. He succeeded in doing so after five minutes of lying on his left side and raising his shoulder by leaning on his left arm. He then complained of a pounding headache, palpitation, dizziness, and severe epigastric pain. His skin was blanched, and he walked about the room doubled over and moaning with pain. The skin was cold and moist, particularly at the extremities. The pupils were somewhat dilated, and the retinal arterioles could be seen to contract and relax. Respirations were increased (16 to 25) and were somewhat deeper; the heart was regular at 130 beats per minute, and a moderately loud, blowing, apical systolic murmur appeared with an accentuated  $A_2$ . The blood pressure rose above 300 mm. Hg systolic (limit of range of the sphygmomanometer) and 160 mm. diastolic, falling to 180 mm. Hg systolic and 150 mm. diastolic within 10 minutes.

A presumptive diagnosis of pheochromocytoma was made, and the patient was admitted to Flower and Fifth Avenue Hospitals on September 8, 1946. The reactions of the patient to the intravenous administration of histamine, tetraethylammonium bromide, and saline were studied preoperatively and are considered in detail later. On September 26, 1946, an 8 by 5 cm. tumor overlying and displacing the superior pole of the right kidney was removed through an oblique right lumbar incision. The pedicle was isolated by blunt dissection and was rapidly ligated, and the encapsulated tumor was removed within four minutes, thus reducing manipulation of the tumor to a minimum.

Since most authors<sup>2,3,4</sup> have reported severe shock following removal of these tumors, several precautions were taken. The patient was given spinal anesthesia of nupercaine, using 5 c.c. of a 1:1500 solution, since the specific gravity of this solu-



tion is lighter than that of spinal fluid. This should result in a relatively greater paralysis of the splanchnic nerves on the right than on the left with the patient lying on his left side at operation. Theoretically, this should produce less anesthesia of the splanchnic nerves on the left and should allow them to continue to function after removal of the adrenal tumor on the right. The blood pressure was 180 mm. Hg systolic and 105 mm. diastolic just before handling of the tumor was begun, and it rose



FIG. 1. Intravenous pyelogram showing pressure effects upon the superior pole of the right kidney by a tumor mass.

to 250 mm. systolic and 130 mm. diastolic during the manipulation necessary to removal. With ligation of the pedicle, the blood pressure promptly fell to shock levels. Intravenous plasma and two 50 mg. intravenous injections of ephedrine brought the reading to 100 to 80 mm. Hg systolic and 70 to 50 mm. diastolic within three minutes. Postoperatively, the blood pressure did not fall below 95 mm. Hg systolic and 55 mm. diastolic, and the pulse rate varied between 100 and 125. Convalescence was rapid and uneventful; the patient was out of bed on the second postoperative day and went home on the tenth postoperative day.

Daily blood pressure recordings for some time thereafter and monthly checkup measurements to date (February, 1947) have not been greater than 130 mm. Hg systolic and 70 mm. diastolic. The patient complained, for about two weeks, of coldness and blueness of his hands and feet, but this symptom disappeared after the administration of 0.1 gram of papaverine four times daily for 10 days. The eye grounds returned to a normal appearance, and the phenolsulfonephthalein excretion was 68 per cent in one-half hour and 77 per cent in one hour, with a total two hour excretion of 77 per cent on October 29, 1946. The patient has had no further attacks and his sense of well-being and libido are completely restored.

*Pathology Report.\** "The tumor is a globular but somewhat irregular, encapsulated mass, weighing 298 grams. Upon the surface, small, pale brown areas, evidently adrenal cortical tissue, can be identified. Upon section, the tumor tissue appears grayish white in some areas and reddish brown in others. The latter discoloration appears to be due to degeneration and hemorrhage. Two cysts are present; these occupy the central half of the tumor, and they are filled with bloody fluid which coagulates upon standing.

"Microscopic examination of the tumor shows a marked variation in the shape of the cells, some being round and oval while others are polygonal. Some of the cells appear light in color, almost hydropic, while others are small and dark staining. There are no definite anaplastic changes seen. The tissue which was fixed in chrome salts has become brown in color. The pathological diagnosis is benign pheochromocytoma (adrenal)."

The tumor contained eight grams of adrenalin in 200 grams of tumor tissue (equivalent to eight liters of a 1:1000 solution of epinephrine). Ninety-eight grams were fluid with a concentration of 100 mg. to 0.1 per cent. The concentration of adrenalin was equal to 4.0 per cent of tissue by weight.†

## DISCUSSION

The patient's reactions to intravenous injections, first of 2 c.c. of a saline solution containing 0.025 mg. of histamine phosphate, then of a solution containing 400 mg. of tetraethylammonium bromide, and finally of 2 c.c. of saline, are compared in figures 2 and 3.

Within one minute after the administration of histamine, the patient developed a typical attack, associated with a rise in blood pressure from 160 mm. Hg systolic and 105 mm. diastolic to 280 mm. systolic and 160 mm. diastolic. The reading returned approximately to normal within five minutes. The pulse rate rose from 94 to 116 and then fell to 96. Although the resting blood pressure was somewhat higher before tetraethylammonium bromide was given, the response was just as pronounced and lasted considerably longer. The reading rose from a basal level of 175 mm. Hg systolic and 105 mm. diastolic to 270 mm. systolic and 160 mm. diastolic in 30 seconds, and the elevation lasted 15 minutes. The pulse rate rose from 75 to 130 and returned to 90. The decrease in the blood pressure when the patient changed from a supine position to standing erect was dramatic, the reading falling from 230 mm. Hg systolic and 125 mm. diastolic to 95 mm. systolic and 80 mm. diastolic. When the 2 c.c. injection of saline was given, no detectable change in the blood pressure or pulse rate occurred.

\* Dr. George K. Higgins, Head of Department of Pathology, New York Medical College, New York City.

† Testing performed by Dr. David Lehr, Head of Department of Pharmacology, New York Medical College, New York City.

On October 15, 1946, approximately two months postoperatively, the above tests were repeated and the patient evinced no reaction whatsoever to the injection of histamine, tetraethylammonium bromide, or saline (figure 4).

It is reasonable to assume that the preoperative hypertension found in this patient resulted from the oversecretion of epinephrine, and that the paroxysmal attacks were due to the sudden release of large amounts of epinephrine into the blood stream. Heavy exertion, positional changes, and manipulation of the tumor all resulted in sudden hypertension of high degree, undoubtedly due to release of epinephrine simply by mechanical pressure on the tumor. Preoperatively, the only times when normal blood pressure readings were obtained were

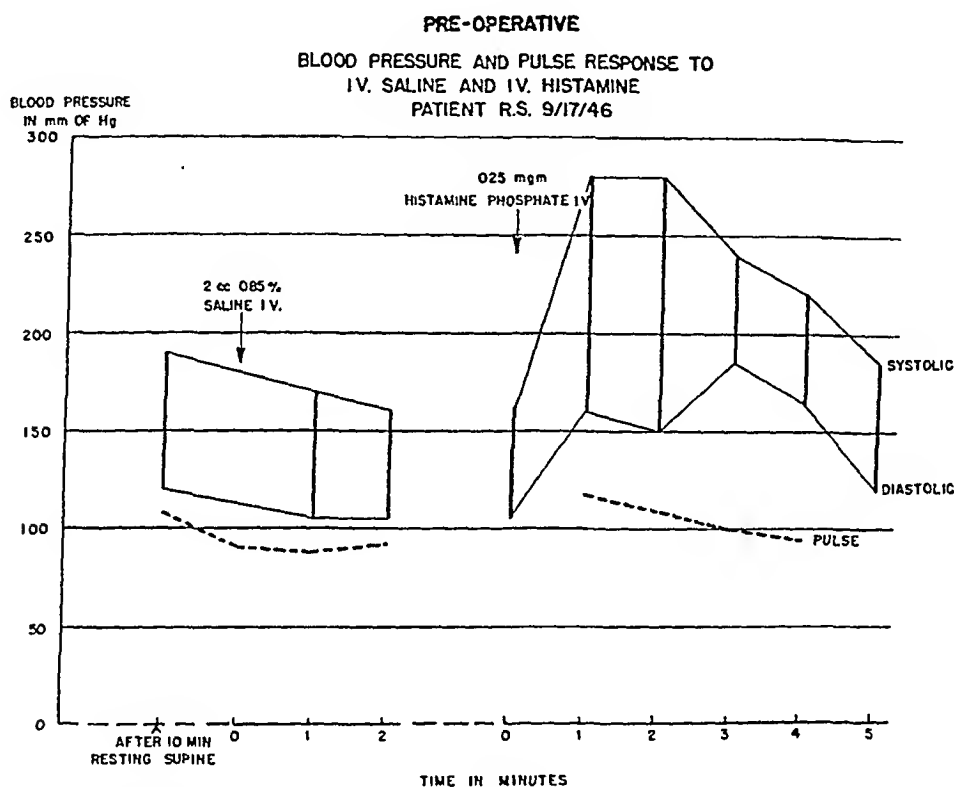


FIG. 2. Graph showing blood pressure and pulse response to the intravenous injection of 0.025 mg. of histamine diphosphate and to the intravenous injection of 2 c.c. of saline.

when the patient had been lying quietly on his back for an hour or more. The effect of massage or pressure in precipitating typical attacks has been emphasized.<sup>1, 3, 5</sup> It is also noteworthy that high concentrations of a pressor-like substance have been found in the blood of patients during seizures.<sup>6</sup>

The release of epinephrine from a pheochromocytoma may be brought about by the dilating action of histamine on the arterioles and capillaries of the tumor. This increases the blood flow through the tumor with resultant outpouring of epinephrine. That histamine may have a direct action on the tumor cells, as it does on the chief cells of the stomach, cannot be affirmed or denied.

Acheson and Moe<sup>7</sup> have demonstrated that tetraethylammonium bromide will block transmission of nerve impulses through the autonomic ganglia. In man, the effects on the cardiovascular system after the administration of 0.2 to 0.5 gm.

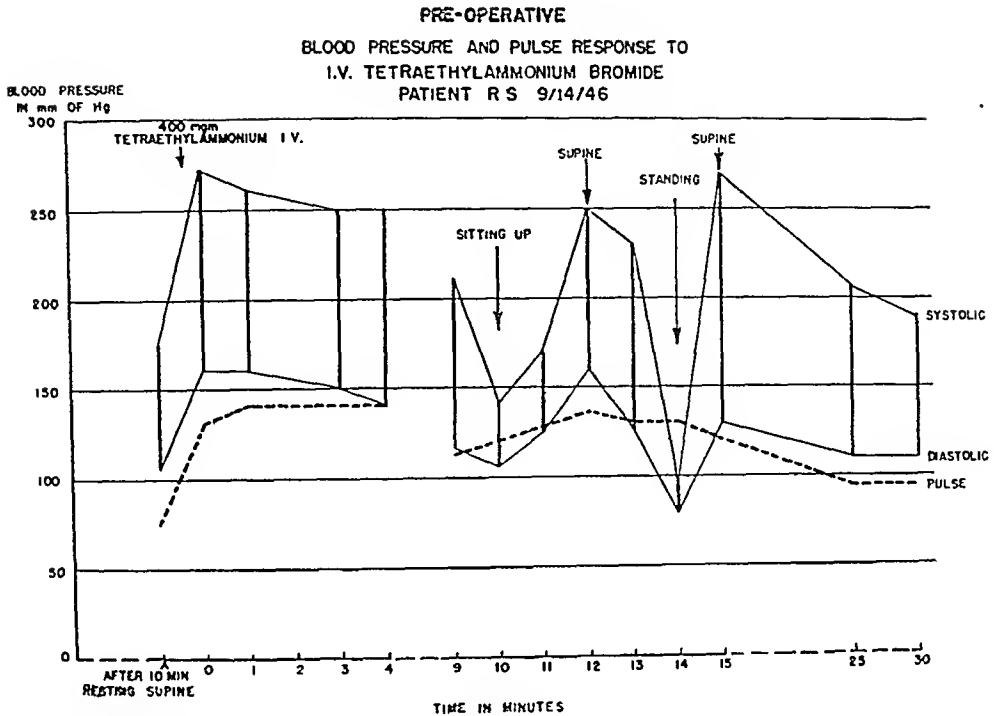


FIG. 3. Graph showing blood pressure and pulse response to the intravenous injection of 400 mg. of tetraethylammonium bromide and to the injection of 2 c.c. of saline. Changes in blood pressure and pulse rate resulting from shifting from a sitting, standing, and supine position are indicated.

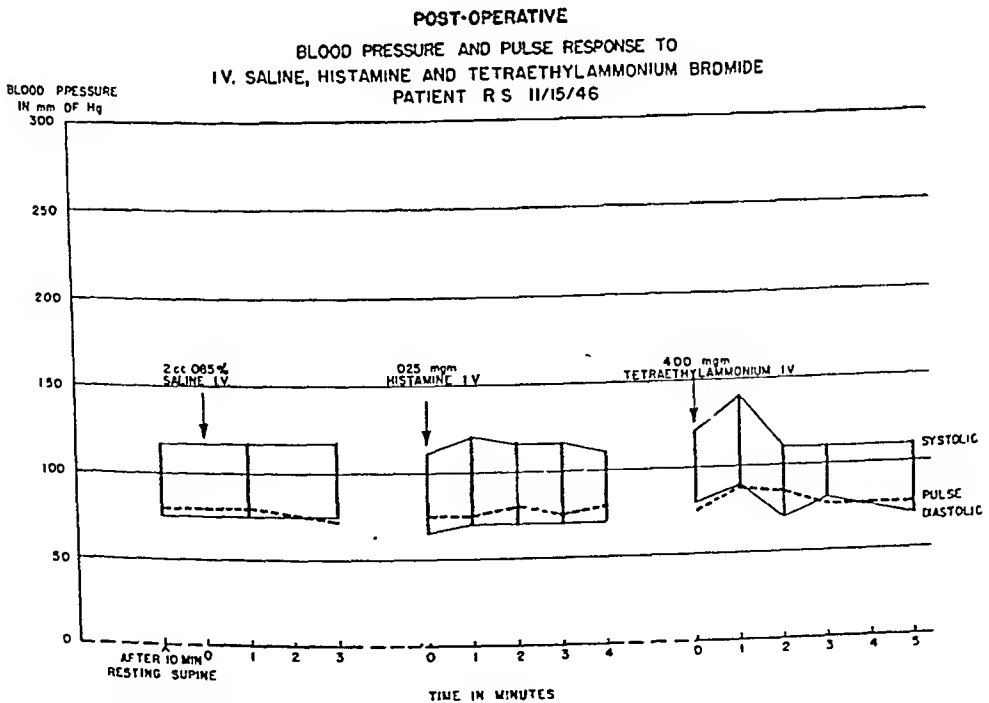


FIG. 4. Graph showing the postoperative absence of response to the intravenous injection of histamine, tetraethylammonium, or saline.

intravenously or up to 20 mg. per kilo intramuscularly are an increase in skin temperature, a transient fall both in systolic and diastolic pressure, postural hypotension, a fall in the peripheral venous pressure, and an increase in the heart rate and cardiac output. These (effects) result primarily from the release of vasoconstrictor tone. Other effects include a cessation of normal peristalsis in the gastrointestinal tract, a diminution in gastric secretion, a decrease in salivary secretion, cessation of sweating, and incomplete dilatation of the pupil with loss of accommodation. The tone of the urinary bladder decreases and the urge to void is abolished. Tetraethylammonium bromide does not inhibit the action of epinephrine. These actions of the drug seem, in the light of present knowledge, to be explained most reasonably as resulting from a blockade of the autonomic ganglia.

However, a blockade of the autonomic ganglia does not readily explain the mechanism of tetraethylammonium bromide in precipitating paroxysmal hypertension in patients with pheochromocytoma. If an excess of epinephrine were constantly present in the patient's circulation, it could be postulated that inhibition by tetraethylammonium bromide of depressor mechanisms under the control of the sympathetic ganglia would result in sudden hyperpiesia. If blockade of the autonomic ganglia results in a denervation of the blood vascular supply of the tumor, loss of vascular tone with vasodilation and increased blood flow might cause an outpouring of epinephrine into the peripheral circulation. A direct vasodilating effect on the arterioles of the tumor would have a similar result. Lyons<sup>8</sup> suggests that the maintenance of renal blood flow in the face of precipitous falls in blood pressure produced by tetraethylammonium bromide can best be explained on the basis of moderate dilatation of the renal arterioles, brought about by blockade of the autonomic ganglia—in effect, a partial denervation of the kidney. Direct stimulation of the secretory cells of the tumor by the drug is unlikely in view of the rapidity (within 30 seconds) with which the blood pressure rises after its intravenous administration.

The use of tetraethylammonium bromide as a test for pheochromocytoma has one advantage over the use of histamine, according to our observations in this one patient. When tetraethylammonium bromide was employed, dangerously high levels of the blood pressure could be controlled simply by having the patient sit up or stand. This resulted in a prompt fall in blood pressure and disappearance of symptoms. Lyons and his co-workers noted this phenomenon in their studies on normal and hypertensive individuals. Hence, it would appear that with the use of a tilting bed or table, tetraethylammonium bromide could be employed with perfect safety in testing for the presence of a pheochromocytoma.

### CONCLUSIONS

1. In a patient with pheochromocytoma the intravenous injection of histamine diphosphate resulted in a typical and uncontrollable attack of paroxysmal hypertension.

2. The same patient responded to the intravenous administration of 400 mg. of tetraethylammonium bromide with a sudden increase in the blood pressure, but the level and duration of the blood pressure rise could be controlled by a change in the patient's posture.

3. The use of tetraethylammonium bromide, therefore, appears to be a safe test for the presence of a pheochromocytoma.

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### SICKLE CELL DISEASE: REPORT OF A CASE WITH CEREBRAL MANIFESTATIONS IN THE ABSENCE OF ANEMIA \*

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SICKLE cell disease was originally described by Herrick<sup>1</sup> in 1910, as anemia with sickle-shaped erythrocytes. During a crisis of sickling these characteristic cells become wedged in capillaries, often producing thrombosis. In the past 20 years increasing attention has centered about the histopathology of sickle cell disease, particularly with reference to the vascular thromboses so frequently noted. This vascular occlusive phenomenon results in a protean symptomatology dependent upon the vessels occluded. Although the cerebral manifestations of the disease were undoubtedly previously noted, the first report was that of Sydenstricker, Mulherin, and Houseal<sup>2</sup> in 1923. This was followed by isolated case reports.<sup>3-22</sup> In 1940 Hughes, Diggs, and Gillespie<sup>23</sup> reviewed the literature on the cerebral manifestations of sickle cell disease and added six cases of their own. Since 1940 additional case reports<sup>24-28</sup> have increased the total reported cases to forty.

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In 1940 Bauer<sup>20</sup> stated that, "The disease known as sickle cell anemia might better be named sickle cell disease, because anemia, though the best known and most frequent sign of this disease, is not the essential and not the most dangerous one." Thus, he suggested that the phenomenon of vascular occlusion could occur independently of anemia as a result of the sickling tendency alone. This concept was further amplified by Bauer and Fisher<sup>20</sup> in 1943.

The case to be presented is of interest because, in a review of the literature of the cerebral manifestations of sickle cell disease, no case has been reported without anemia in which the clinical and pathological manifestations were predominantly cerebral.

#### CASE REPORT

A 20 year old colored male was admitted to the United States Naval Hospital, Newport, Rhode Island, on August 20, 1944, complaining of dizziness and pain in the right arm. He was drowsy and his response to questioning was abnormally slow. The temperature was 100° F., pulse 100, and respirations 28. Past and family histories were negative. Physical and neurological examinations showed only fever, slowness of cerebration, and drowsiness.

Because of the impaired sensorium a spinal puncture was done. The spinal fluid was slightly, but homogeneously blood-tinged, and under a pressure of 120 mm. of water. There was no growth on culture. Spinal fluid chemistries were as follows: sugar, 75 mg. per cent; total protein 88.8 mg. per cent.

For the next three days his only symptom was mild generalized headache. The temperature ranged from 97° F., to 100.8° F. Blood studies were as follows: Hemoglobin, 15 grams (Sahli); erythrocytes 4.95 million; leukocytes 13,800 with 70 per cent polymorphonuclear neutrophils, and the remainder of the differential formula, normal. The serological test for syphilis was negative. Tests for sickling were not done.

On the fourth hospital day he had a generalized convulsion. The temperature rose rapidly to 108° F., rectally, and the pulse to 220. During the next eight days his condition remained static. He was in deep coma. The temperature varied from 101° F., to 105° F.; pulse from 110 to 180, and respirations from 35 to 80 per minute. Repeated neurological examinations are summarized in the following findings. Cranial nerves: The fundi revealed no abnormality of either discs or vessels. The pupils were equal in diameter and reacted sluggishly to light. There was a spontaneous nystagmus, horizontal in type. The remainder of the cranial nerves showed no abnormality. Motor system: Sporadic clonic convulsive movements of the right side of the body were noted. The left arm remained in a state of tonic extension. Intermittent fibrillations were noted in the muscles of the right thigh. Deep tendon reflexes were hyperactive on the left side and normal on the right. All superficial reflexes were absent. There was no response to plantar stimulation. Sensory system: None of the modalities of sensation could be tested.

Treatment consisted of oxygen therapy, sedation with the anticonvulsants, and general supportive measures. Ice caps, alcohol sponges, and ice water enemata were employed to combat hyperthermia. In spite of these measures he suddenly died on the thirteenth day following admission.

An autopsy was performed immediately after death. The body was that of a tall, thin, colored male, 20 years of age. Examination of the skin disclosed no abnormalities. No hemorrhages were noted. A summary of the gross pathologic findings follows: There were 1000 c.c. of cloudy fluid in the left pleural cavity. A small, recent hemorrhagic infarct was seen at the base of the left lung. The spleen weighed 110 grams and presented a friable cut surface. The liver weighed 1850 grams and showed a smooth, reddish-brown, lobulated cut surface. The remainder of the abdominal and thoracic viscera were grossly normal.

Microscopic studies of the liver, spleen, heart, lung, and kidneys, showed the vessels packed with sickled erythrocytes, estimated to be almost 90 per cent of the total number present. Occasional normoblasts were observed.

The epicardium was smooth. The cardiac fibers were fragmented in many places, and throughout the myocardium there were found many areas of focal degeneration.

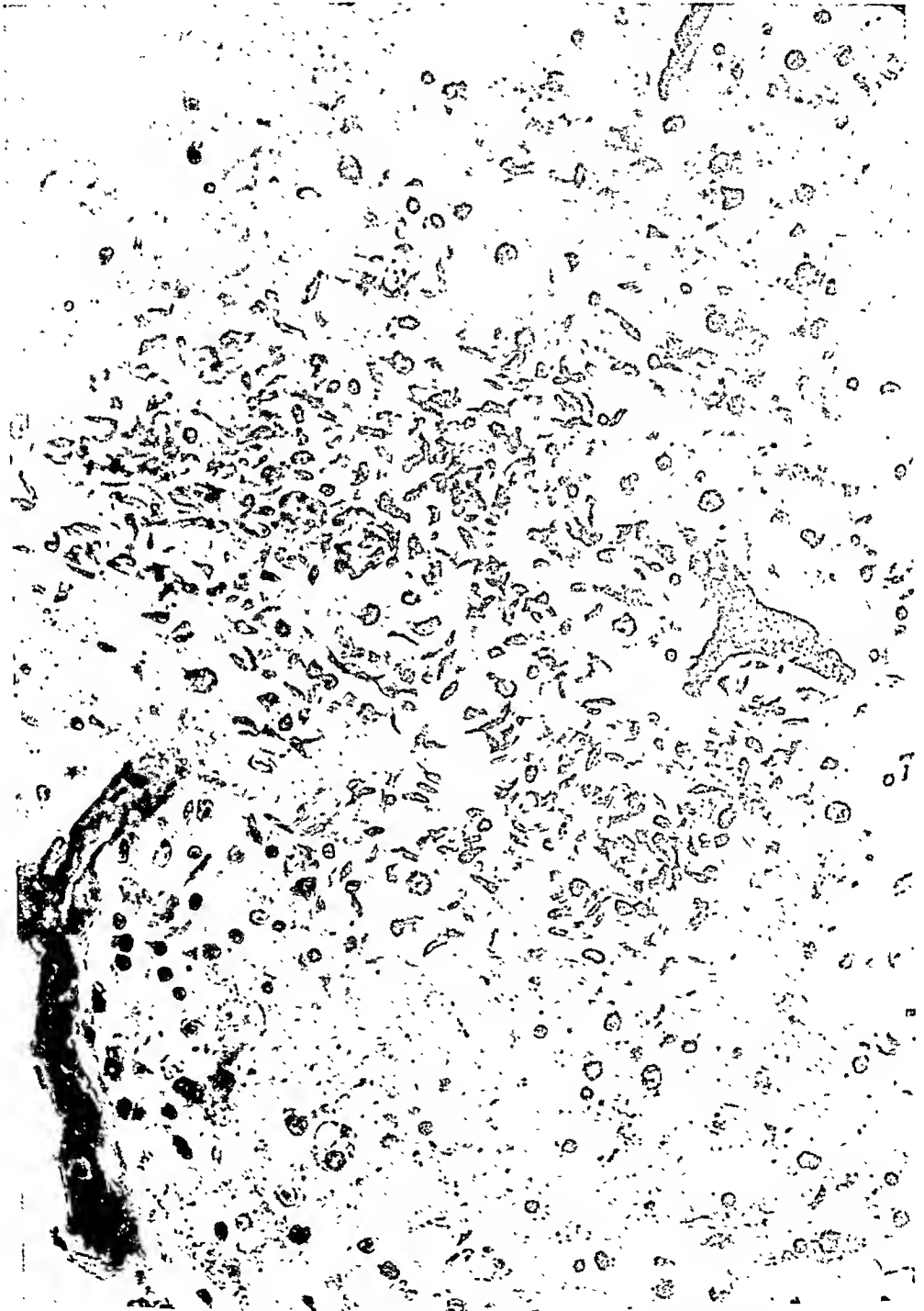


FIG. 1. Photomicrograph showing closely packed sickled erythrocytes in an area of hemorrhage.



In these areas the muscle fibers had disappeared, leaving only the sarcolemma and occasional pyknotic nuclei. There was much interstitial edema. Within the kidneys numerous punctate hemorrhages were found. In the liver the architecture was preserved. There was slight cloudy swelling of the cord cells. The hepatic and Küpffer cells showed mild pigmentary changes. No abnormalities of the splenic capsule or trabeculae were seen. There was diffuse congestion of the sinusoids in the red pulp. This was most pronounced near the splenic corpuscles. A few scattered areas of hematopoiesis were noted. There was questionable endothelial proliferation within the splenic vessels. The pleural surface of the left lung was covered with a heavy deposit of leukocytes and fibrin. A histologically typical fresh hemorrhagic infarct was seen within the lung tissue beneath this area. Although the pulmonary arteries, veins, and capillaries were packed with sickled cells, no thrombi were noted in the vessels examined microscopically.

When the calvarium was opened, no bony abnormalities were observed. The dura was intact. Examination of the brain *in situ* showed extreme congestion, tortuosity, and dilatation of all of the cortical veins, which were cord-like and tense. The cerebral convolutions appeared swollen and flattened. Numerous scattered subpial, petechial hemorrhages were seen over the frontal and occipital lobes. An excess of cerebrospinal fluid was present in the subarachnoid space.

Serial coronal sections through the brain revealed numerous wedge-shaped areas of yellowish softening surrounded by confluent groups of petechial hemorrhages involving the cortical gray matter and the adjacent white matter in both cerebral hemispheres (figure 1). These hemorrhagic areas varied in diameter from 1 to 3.5 cm. The deep cortical white matter of the cerebrum, as well as the basal ganglia, midbrain, pons, and cerebellum, revealed only scattered petechial hemorrhages. A few fresh confluent hemorrhages were found in both cerebral peduncles. The medulla and a small portion of the cervical spinal cord showed no gross pathologic change.

Microscopic examination of the sections of the cerebral cortex showed an organizing thrombotic process distinctly limited to the vessels in the subarachnoid space, pia mater, and the vessels lying within the cortical gray matter. Innumerable veins of all sizes were occluded. These thrombi were distinctly *ante mortem*. Many of the veins were surrounded by broad cuffs of confluent hemorrhage. Some of these hemorrhagic areas appeared recent; others showed partial resolution. The endothelium of the cortical veins had proliferated, appeared loosened, and was turned inward toward the lumen of the vessel to become incorporated within the thrombus in many places. Much edema of the vessel walls was present and there was an associated infiltration of polymorphonuclear leukocytes, lymphocytes, and macrophages. Numerous areas of partially organized subarachnoid hemorrhage were seen. There was extensive destruction of ganglion cells throughout the cortex. Glynn stains for bacteria were negative. Following the suggestion of Wade and Stevenson,<sup>26</sup> sections of the cortex were stained for fat. Numerous fat laden gitter cells were found, but no intravascular fat droplets were seen. Sections taken at other sites throughout the brain showed a picture similar to that described above.

**Anatomical Diagnosis:** Sick cell disease; congestion, spleen; evidence extramedullary hematopoiesis; endothelial hyperplasia, cortical vessels, marked; thrombosis, cortical veins; perivascular and confluent interstitial hemorrhages, cortex, marked; with encephalomalacia, secondary, mild; pulmonary infarct, recent, hemorrhagic; focal degeneration, myocardium; hemorrhages, petechial, kidney.

## DISCUSSION

Initially the patient presented a vague clinical syndrome composed only of mental retardation, drowsiness and slight fever. The physical examination was



FIG. 2. Segment of cerebral cortex showing confluent petechial hemorrhage.

negative. The spinal fluid contained fresh blood. The clinical syndrome was that of an atypical spontaneous subarachnoid hemorrhage. On the third hospital day signs of cerebral cortical irritation appeared in the form of generalized convulsions. This was rapidly succeeded by clinical signs of diencephalic damage.

At this point it was evident that the syndrome resulted from diffuse involvement of the central nervous system. There then developed an acute diffuse hemorrhagic encephalitis, the etiology of which remained obscure. Diagnosis was not established until autopsy, when the sickled intravascular erythrocytes, and the associated vascular and thrombotic lesions were demonstrated.

The entire pathologic process in this case was vascular in nature. At no time was there laboratory or clinical evidence of anemia or of a hemolytic crisis. The major lesions were limited to the cortical veins which were filled with laminated, recent thrombi composed of sickled red cells. The pathologic process which resulted from this occlusion was that of an intense passive congestion of the cortical veins and capillaries with subsequent rupture or erythrocytic diapedesis which produced diffuse, confluent destructive cortical hemorrhages (figure 2). These hemorrhages had been present for a length of time sufficient for mild early reactive gliosis to occur. No arterial occlusions were observed.

This intense passive congestion produced a stagnant anoxia which further relaxed the vessel walls. This process in turn resulted in increasing hyperemia and vascular permeability, thus augmenting the bleeding caused by the venous thrombotic lesions. The evident venous origin of the cerebral lesions would tend to discredit the theory that the cortical hemorrhages seen in the cerebral manifestations of sickle cell disease result from fat emboli.<sup>20</sup>

This case demonstrates the value of the routine examination of the blood (and bloody spinal fluid, if present), for sickling in any patient presenting obscure neurologic signs which might be explained by diffuse, or focal venous thromboses. It is important to consider the diagnosis of sickle cell disease in any obscure neurologic lesion in the negro.

Anemia is not necessarily a part of the picture of sickle cell disease, and this case demonstrates that it is not necessarily a part of sickle cell disease in which the symptomatology is predominantly cerebral. A blood dyscrasia might have been suspected if anemia had been present.

### SUMMARY

A case of sickle cell disease without anemia is presented in which the signs and symptoms were solely referable to the central nervous system. The value of routine sickling tests on all patients presenting evidence of subarachnoid bleeding or neurologic symptoms which might be explained on the basis of a diffuse vascular thrombotic process has been emphasized.

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## SICKLE CELL ANEMIA WITH STRIKING ELECTROCARDIOGRAPHIC ABNORMALITIES AND OTHER UNUSUAL FEATURES, WITH AUTOPSY \*

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THIS case of sickle cell anemia with autopsy is considered worthy of reporting because of the following unusual features: (1) the symptomatology simulating coronary occlusion, with gross electrocardiographic evidence compatible with this condition, in the absence of any histopathologic evidence of myocardial damage other than simple cardiac hypertrophy and dilatation with moderate interstitial edema; (2) the marked sickling of erythrocytes even in the usual blood smear; (3) the coexistence of duodenal ulcer which evoked abdominal pain simulating that often seen in hemolytic crises of sickle cell anemia; (4) the extraordinarily small size of the spleen (5 grams).

### CASE REPORT

*History.* A 22 year old negro was admitted August 13, 1946 to a Naval Hospital 11 hours after the onset of a severe substernal chest pain. Eight days prior to the onset of the chest pain, the patient developed cramp-like intermittent lower abdominal pain, anorexia, vomiting, fever, and chilly sensations associated with yellow sclerae and dark urine. On the morning of admission while at work he was suddenly seized by severe substernal pain. The pain did not radiate or subside and, at the time of admission to the hospital from a Naval dispensary, was more severe than at its onset. Physical examination soon after the onset of the pain disclosed an acutely ill patient with deeply jaundiced sclerae, a heart enlarged to the left and right and a basal systolic murmur loudest in the pulmonic area and along the left border of the sternum. The blood pressure was 174 mm. Hg systolic and 114 mm. diastolic in the right arm and 180 mm. systolic, 120 mm. diastolic in the left arm. At this time a chest film showed the heart enlarged in all diameters, predominantly the left ventricle, with increased hilar markings in the right upper lobe. Examination of the blood showed a marked anemia and sickling. The temperature was 98.4°, pulse 88 and the respirations 24. The impression was sickle cell anemia with hemolytic crisis, and accordingly the patient was transferred to the hospital.

The family history revealed no evidence of sickle cell anemia in other members of his family. Blood studies at this hospital on an older brother failed to reveal even a sickle cell trait.

The past history revealed that the patient was hospitalized as a child because of

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The opinions herein stated are those of the authors and not necessarily those of the Medical Department of the U. S. Navy.

jaundice of unknown cause. Subsequently he had attacks of abdominal cramps but never severe enough to prompt medical attention.

After the patient entered the Navy in 1942 he was hospitalized because of jaundice, joint pains, and abdominal cramps. He was found to have sickle cell anemia. He was transfused several times and was subsequently discharged from the Naval service. In 1944 and 1945 the patient had two episodes of similar symptomatology for which hospitalization was required.

*Physical Examination.* On admission, examination revealed a well developed, emaciated young negro with a tower-shaped skull, deeply icteric sclerae and pale mucosae, appearing acutely ill, lying flat in bed. At this time, the blood pressure was 144 mm. systolic and 80 mm. diastolic, the temperature was 100.4°, the pulse 78 per minute and respirations 18 per minute. A grade IV (I-VI) basal systolic murmur was heard, at the greatest intensity in the pulmonic area. The radial and brachial arteries were readily palpable and extremely firm. There was tenderness in the mid-epigastrium with moderate generalized splinting of the abdomen. Several pretibial oval shaped scars were present over the lower extremities.

*Laboratory Findings.* Routine stained blood smears showed up to 20 per cent sickled cells, whereas 100 per cent sickled cells were observed in repeated wet preparations after 24 hours. A blood count showed 2.5 million red blood cells, with 7.2 grams of hemoglobin, and a white blood cell count 15,100 with an essentially normal differential count. The red blood cell fragility test showed beginning hemolysis at 0.40 per cent sodium chloride which was incomplete even in distilled water (control hemolysis began at 0.44 per cent and was complete at 0.28 per cent). A van den Bergh test was indirect and a serum bilirubin was 15 mg. per cent. Urine urobilinogen was positive up to 1-100 dilution. Urinalysis showed a specific gravity of 1.013, 50 mg. per cent albumin, 3 to 5 white blood cells and 8 to 12 red blood cells per high power field. The Kahn test was negative for syphilis. Erythrocyte sedimentation rate (Cutler) on August 13, 1946 was 9 mm. per hour.

An electrocardiogram on admission (figure 1) showed a rate of 80 with regular sinus rhythm, PR interval of 0.13, left axis deviation, with T<sub>1</sub> low, M-shaped and flattened, T<sub>2</sub> isoelectric, T<sub>3</sub> inverted and T<sub>4</sub> upright. It was interpreted as evidence of possible myocardial damage.

Teleroentgenogram showed a heart grossly enlarged in all diameters, especially in the region of the left ventricle.

*Clinical Course.* The substernal pain was only partially relieved by morphine. After the patient was kept in an oxygen tent for four days, he was free of chest pain but complained of pain in the midepigastrium, especially at night, as well as pain in his knees and elbows. The epigastric pain was relieved by sodium bicarbonate and by milk. He stated that he was accustomed to taking these in large quantities for the past several months. The patient was placed on a modified Sippy regime with some benefit, although it was undecided as to whether the abdominal pain was a result of the hemolytic crisis and favorably influenced by alkaline therapy, or due to a peptic ulcer. Fluoroscopy showed no abnormalities other than a heart enlarged in all diameters. After the crisis had subsided a transfusion was given with no apparent signs of reaction or definite benefit. Gastrointestinal studies were ordered but before the patient could recover sufficiently to warrant radiographic examination he had another severe crisis on the forty-first hospital day. He complained of severe substernal, epigastric, lumbo-sacral, knee and lower leg pain. The heart was extremely overactive with a bounding pulse and heaving precordium. The pulmonic murmur was increased to Grade V and there was a systolic thrill in the pulmonic area. The patient was given morphine therapy in  $\frac{1}{4}$  gr. doses every two to four hours, with only partial control of pain. He was again placed in an oxygen tent. A second electrocardiogram on August 15, 1946 (see figure 1), showed some progression of the

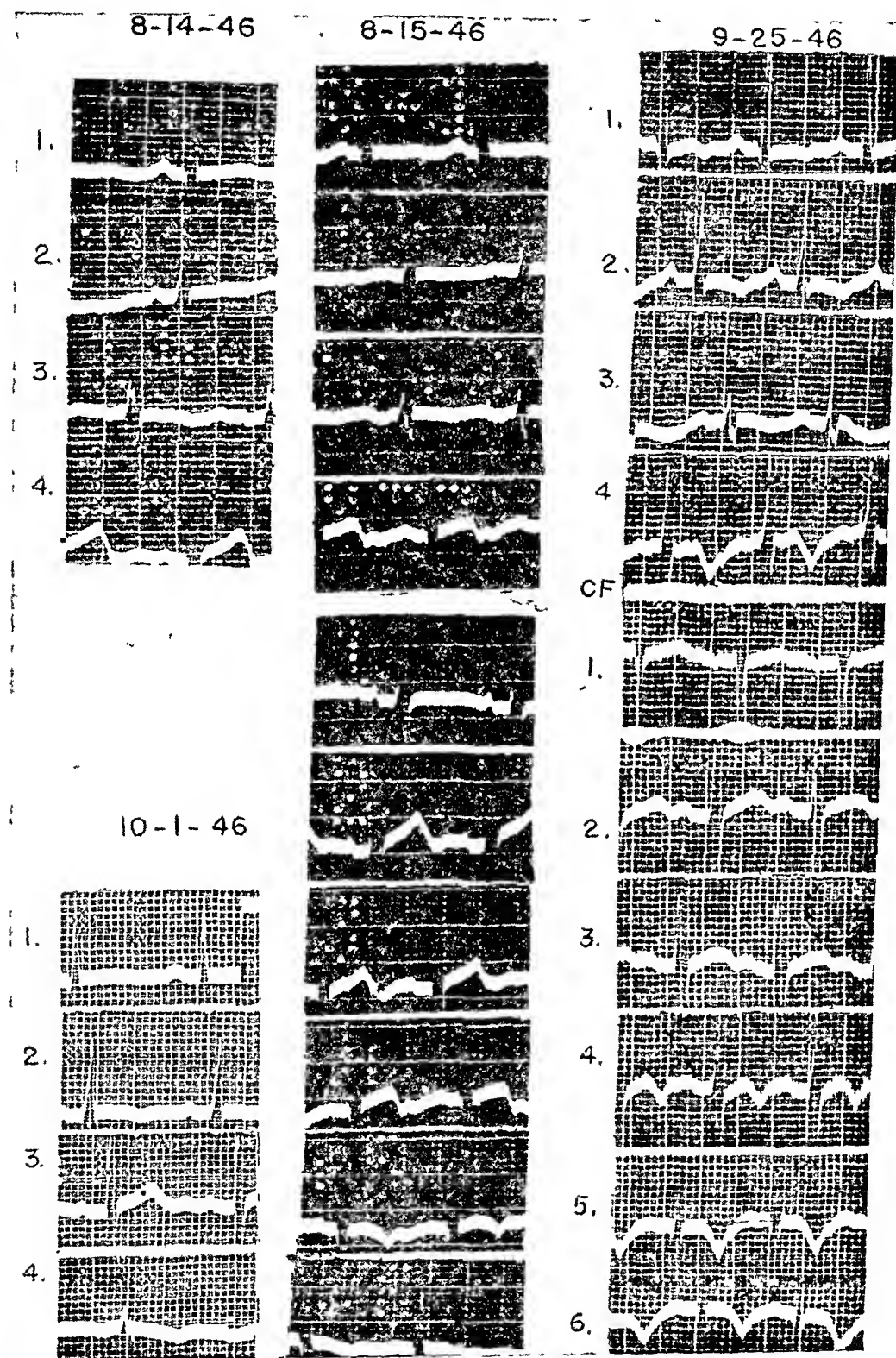


FIG. 1. Successive electrocardiographic tracings.



changes noted in the initial tracing of August 14, 1946. The T-waves in Lead I were further depressed, T<sub>2</sub> isoelectric, T<sub>3</sub> inverted and T<sub>4</sub> showed terminal inversion with decreased amplitude. Chest leads showed T-waves inverted in CF 5 and 6. The electrocardiogram on September 25, 1946 (figure 1), the day following the onset of the second crisis, showed further gross changes: T-waves in Lead I were diphasic, T<sub>2</sub>, T<sub>3</sub> and T<sub>4</sub> were inverted, and the chest leads showed inversion of T-waves in CF 4, 5, and 6. The tracing of October 1, 1946 (figure 1), six days following the onset of the second crisis and three days after he had improved, showed T-waves in Lead I again upright but of low amplitude, with T<sub>2</sub> and T<sub>3</sub> inverted and T<sub>4</sub> again upright.

The erythrocyte sedimentation rate (Cutler) on September 6, 1946 was 12 mm. per hour. On September 25, 1946 it was 27 mm. per hour and 4 mm. in 5 minutes. The temperature fluctuated irregularly from 98° F. to 101° F. for the first two weeks and then ranged from 97.5° F. to 100.5° F. for the next four days during the second crisis. It then gradually dropped to normal. On October 8, the patient entered his third severe crisis and his temperature rose and remained at 102° F. for 24 hours and then rose to 103° F. on the day of his death, October 10, the fifty-eighth hospital day. The pulse previously had averaged 85 per minute, rising to 100 during the two previous crises. It ranged from 110 to 120 per minute during the last 24 hours. The respirations which had averaged 20 to 25 per minute rose to 30 to 45 per minute during the last day. These observations plus the findings of moist râles throughout the chest indicated a terminal pneumonia rather than congestive failure, as the contributory cause of death.

Autopsy examination revealed the following pertinent findings:

The heart weighed 455 grams and showed right and left ventricular enlargement. There was moderate dilatation of both auricles. Eighteen representative sections were examined microscopically. These included ten from the area of questionable pathology as indicated by the electrocardiograms. All sections revealed moderate hypertrophy of some muscle fibers. Three quite small areas of fibrosis were noted. There was moderate interstitial edema. Occasional clumps of about five Anitschkow cells were observed. These were in the interstitial tissue about the vessels and capillaries. There was no evidence of thrombosis, endarteritis, polymorphonuclear or fatty infiltration or degeneration.

The lungs, grossly and microscopically, revealed the findings typically associated with bronchopneumonia.

The spleen weighed five grams. It measured 6 by 1.5 by 0.3 cm. It was light green and quite firm. Microscopic examination revealed complete replacement of the normal parenchyma by irregular masses of hyalinized fibrous tissue and thick walled fibrotic blood vessels. The fibrous tissue and vessel walls were infiltrated with amorphous material which contained calcium and iron. In the vessels this material was located particularly in the internal elastic membrane. The arteries and arterioles were distorted by these hemosiderotic masses. No hemopoiesis was observed.

The abdominal lymph nodes showed marked hypertrophy grossly. Microscopically hyperplasia of the reticulo-histiocytic elements was noted.

The bone marrow of the skull, sternum, ribs, vertebrae, femur and tibia was markedly hyperplastic. The hyperplasia had caused marked thinning of the inner and outer tables of the skull. The marrow of about one-half of the ribs was hyperplastic while the marrow of the others showed extensive fatty infiltration. One area of the cortex of the anterior surface of the upper third of the right tibia was thinned to 0.1 cm. In the center of the thinned area there was a thrombosed penetrating vessel. Surrounding the vessel and extending over a radius of 3 cm. was a collection of dark brown semi-fluid material. This was located between the cortex



and periosteum. Microscopic examination proved it to be essentially normal bone marrow.

The liver weighed 2270 grams. It was moderately congested. The K pffer cells contained large amounts of iron pigment. The architecture was well preserved.

The kidneys showed multiple old and recent infarcts. Microscopic examination revealed moderate congestion of the parenchyma and extensive iron deposition in the convoluted tubules.

The duodenum revealed a 1.0 cm. in diameter active ulcer.

The blood in all the organs showed marked sickling and many nucleated red blood cells.

### DISCUSSION

In contrast to the gross electrocardiographic abnormalities in our case, an analytical study of electrocardiograms of 25 patients with sickle cell anemia by Winsor and Burch<sup>1</sup> revealed no inversion of the T-waves in Lead I (average amplitude 1.7 mm.) or Lead II (average amplitude 4 mm.), and upright T<sub>s</sub> waves in 70 per cent of the cases, with no sharp inversion in any case. In the chest leads the average amplitude of the T-waves in Leads CF-1, CF-2, and CF-3 was - 3.4, - 3.6 and 1.5 mm. respectively. In Leads CF-4, CF-5 and IVF the T-waves were inverted or diphasic in 40 per cent of the subjects. In Case 16 of their series, one of four followed by serial electrocardiograph for three to four years, there were progressive abnormal changes but the other three were normal. In Case 16 the T-waves in Lead IV were normal and upright on August 14, 1939 and November 12, 1941 but deeply inverted on December 3, 1941 and May 3, 1943. They do not state whether the patient had a crisis during his electrocardiographic changes or whether reversion toward normal occurred. Twenty per cent of 25 cases showed significant electrocardiographic changes when single tracings were studied in the usual manner; 4 per cent showed a low T<sub>1</sub>.

Klinefelter<sup>2</sup> found no frank electrocardiographic evidence of myocardial damage, on the other hand, in his 12 patients with sickle cell anemia.

Zimmerman and Barnett<sup>3</sup> have reported a case of sickle cell anemia simulating coronary occlusion. This case was that of a 30 year old negro male with proved sickle cell anemia and a coronary-like syndrome. Severe substernal pain radiating to both arms was accompanied by profuse perspiration, nausea and vomiting. The admission electrocardiogram revealed an inverted T-wave in Lead IVF and broad and low T-waves in Leads I and II without any significant ST segment deviation. In a second tracing taken three days after admission the T-waves in IVF were M-shaped and the T-waves in Lead II diphasic. The third electrocardiogram taken 16 days after admission and shortly before discharge, showed an upright T<sub>4</sub> with an increase in amplitude of the upright T-wave in Leads I and II. The electrocardiographic changes in the case we are reporting were more gross than those of the above case, especially in the tracing of September 25, 1946 (figure 1) which was taken one day after the onset of the second severe crisis. However, in our case, as was noted in their tracings, the pattern reverted toward normal much sooner than one would expect in the case of an infarction. The tracing of October 1, 1946 which is reverting to normal was taken six days following the previous tracing of September 25, 1946 and only three days after the remission from the second crisis.

In the aforementioned study of 25 patients with sickle cell anemia, nine were autopsied, three dying in congestive heart failure. All nine cases showed, in ad-

dition to variable degrees of cardiac hypertrophy and dilatation, one or more of the following pathological changes: interstitial edema, myocardial degeneration, vacuolated sarcoplasm, Zenker's degeneration, polymorphonuclear interstitial infiltration, and in one instance, obliterative endarteritis of the coronary and pericardial vessels. The heart weights ranged from 225 to 440 grams.

Winsor and Burch<sup>1</sup> state further that while cardiac hypertrophy and dilatation, often associated with fatty degeneration, is common in a variety of severe anemias, there are certain changes in sickle cell anemia which are not due to anemia. They state that changes in the heart may be manifestations of arteritis and endarteritis with thrombosis.

These pathologic cardiac findings were in contrast to those in our case which merely showed simple hypertrophy, slight dilatation, and moderate interstitial edema, despite careful search for other changes, including 10 sections through the left ventricular wall at the site in which myocardial damage was anticipated from the electrocardiographic changes. The three small areas of fibrosis might be expected with the degree of hypertrophy noted. No significant interpretation can be attached to the Anitschkow cells, but it is believed that they bear no relation to the sickle cell anemia.

Wintrobe,<sup>4</sup> referring to the studies of Carter and Traut,<sup>5</sup> and Ellis and Faulkner,<sup>6</sup> has summarized the commonest electrocardiographic changes, often reversible, occurring in severe anemia of any type as depression of R-T (S-T) junction with a U-shaped deformity of the S-T segment and flat or inverted T-waves, but without corresponding changes in QRS complex. He states that these electrocardiographic changes have been similar to those in sickle cell anemia. He stresses the fact that the heart in sickle cell anemia, which is enlarged in at least 76 per cent of the cases, represents the extreme form of the "heart in anemia," whatever the mechanism may be. He refers to various possible etiologic factors such as increased work load, chronic myocardial anoxia, the circulatory stasis in the internal organs presumably due to sickling, the characteristic extreme tortuosity of the blood vessels, disseminated occlusions of small pulmonary arteries leading to cor pulmonale, etc. At any rate, with respect to the heart in anemia in general, he is of the opinion that anemia of short duration results in cardiac dilatation that can be completely overcome by relief of the anemia (cf. similar reversibility of electrocardiographic changes), whereas in cases of long duration hypertrophy takes place.

In view of the above consideration, it seems reasonable to conclude that in our patient, whose anemia remained relatively stable at 6 to 7 grams of hemoglobin, the augmented electrocardiographic abnormalities during crisis were due, in large measure at least, to the relatively increased myocardial anoxia imposed by the greater work demands on the heart incident to the fever, pain, etc. which occurred with each crisis. This case was considered no exception to the general observation<sup>4</sup> that sickle cell anemia patients are not improved by blood transfusion. Furthermore, the cardiac pathology of simple hypertrophy, etc. in this case was little more than that commonly seen in other severe anemias.<sup>5, 6</sup>

The lack of more cardiac pathologic changes in our case was all the more surprising in view of the marked sickling, up to 20 per cent on the stained smear, an observation which is uncommon,<sup>7</sup> occurring only in very severe cases.

Various causative factors in the abdominal crisis of this disease have been suggested, such as gall stones,<sup>8, 9</sup> arterial thrombosis of the liver,<sup>10</sup> the commonly

observed hypochlorhydria,<sup>11, 12</sup> splenic infarcts,<sup>12</sup> and root pains on the basis of marked changes in the vertebrae.<sup>13</sup> In our patient undoubtedly some of his pain was caused by his duodenal ulcer, which was not strongly suspected. We have been unable to find any reported case in which a peptic ulcer coexisted with sickle cell anemia, which leads us to assume that no causal relation exists. However, the infarctions frequently observed in other organs in this disease might offer a theoretical reason for this patient's ulcer, although thrombotic occlusion of this deep chronic ulcer was not demonstrable. The alkaline therapy given to him ameliorated his epigastric pain to the extent that he continually asked for sodium bicarbonate and milk; his lower abdominal pain and flank pain, however, were not relieved. It is of interest here that Levy and Schnabel<sup>14</sup> reported immediate cessation of all abdominal pain in a patient with sickle cell anemia on two occasions following administration of sodium bicarbonate, potassium citrate and potassium sulfocyanate, but no change in the sickle cell count was observed at these times.

The smallest spleen in sickle cell anemia has been reported as weighing 2.4 gm. To our knowledge, the spleen in our case which weighed 5 grams, is the second smallest to be reported. The specific pathological changes observed in larger spleens by Rich<sup>16</sup> and Diggs<sup>17</sup> were not found in our case, presumably because of the extensive fibrosis.

#### SUMMARY

An unusual case of severe sickle cell anemia is presented. The gross electrocardiographic changes, even though quickly but partially reversible after the hemolytic crises, led us to expect rather marked myocardial damage, but an autopsy revealed only the simple hypertrophy and moderate interstitial edema often seen in a variety of severe anemias.

A coexisting duodenal ulcer was a confusing element in the clinical picture.

The weight of the spleen in this case was 5 grams, the second smallest reported in the literature.

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## HYPERTHYROIDISM OCCURRING AT AN EARLY AGE IN DISSIMILAR TWINS \*

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HYPERTHYROIDISM is a disease which may occur during childhood and adolescence. Pemberton and Black<sup>1</sup> have reported 189 children of 14 years and under who were observed at the Mayo Clinic while suffering from this disease. Over 80 per cent of their patients were between the ages of 10 and 14 years, and they found the disease to be rare before the age of nine years. A perusal of the literature reveals a sufficient number of articles on the subject to justify a brief discussion of the salient points of the disease in childhood and adolescence before presentation of the two cases which instigated this report. The statements made refer to patients 14 years of age and under.

In all series female patients predominate, the sex ratios in three comparable series<sup>1, 2, 3</sup> averaging 5.7 to 1. Some authors<sup>4</sup> believe that a family history of thyroid disease is unusually frequent in patients in this age group.

With few exceptions the symptomatology parallels closely that of the adult disease.<sup>5</sup> An abrupt onset is frequent, and emotional instability may be a most troublesome accompaniment.<sup>8</sup> This was strikingly evidenced in one of the cases here reported. Several authors have been impressed with the frequency of exophthalmos. Helmholtz<sup>6</sup> found this condition present in 83 per cent of his cases; Greene and Mora<sup>10</sup> in 81 per cent of their cases. Crile and Crile<sup>9</sup> concluded that exophthalmos was more frequent and more severe in children and that failure to recede postoperatively was not uncommon.

For many years it has been realized that a normally functioning thyroid gland is essential for normal growth, and hyperthyroidism occurring before the attainment of growth maturation is frequently associated with an increased rate of growth.<sup>3, 6, 7</sup> Striking precocious skeletal development at the expense of soft tissue development may occur,<sup>6</sup> and Hertz<sup>7</sup> has observed a case showing such a striking degree of growth as to be termed "thyrotoxic gigantism." Hertz et al.<sup>7</sup>

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have studied the problem of hyperthyroidism and growth and conclude that the excess of hormone apparently does not produce early or late epiphyseal closure, so that the acceleration occurs only during the normal growth span.

Burke<sup>10</sup> has reported a hyperthyroid child who after four and one-half months of thiouracil therapy was showing a satisfactory response. Prior to the introduction of this drug, and there is as yet no other report available on its use in patients of this age, subtotal thyroidectomy following careful preoperative preparation with iodine was the procedure advised in a vast majority of the cases. The possibility of permanent personality changes due to the associated emotional instability, the frequency of abnormal growth rates, and the natural lack of coöperation on the part of the patient usually preclude long term medical therapy. Severe operative and postoperative reactions are frequent, and the necessity of multiple stage operations is increased. Some authors<sup>1, 12, 13</sup> have stressed the frequency of postoperative hypothyroidism, but in many cases continued observation has shown this to be a transient phenomenon. Others stress the frequency of recurrence or persistence of the disease,<sup>11</sup> and these appear to be more frequent sequelae than hypothyroidism. The capacity for regeneration in thyroid glands of patients in this age group and the highly satisfactory response to thyroid in states of hypofunction recommend a more radical type of operation.

In 109 cases prepared for operation with iodine, Pemberton et al.<sup>1</sup> report a mortality of 2.8 per cent. Dinsmore<sup>13</sup> operated on 43 patients with two deaths after similar preparation.

Hyperthyroidism has been reported to occur in unusually early age groups. Warren and Shpiner<sup>14</sup> have reported primary hyperplasia of the thyroid gland in one of still-born twins from a mother who was five months pregnant and who aborted three days after a second partial thyroidectomy for moderately severe hyperthyroidism. White<sup>15</sup> has studied a fetus with primary hyperplasia of the thyroid gland whose mother was hyperthyroid, and Ochsner and Thompson<sup>16</sup> have observed this condition in an infant born of a hyperthyroid mother. Detailed reports have appeared on children five years of age and under with classical hyperthyroidism cured by subtotal thyroidectomy.<sup>4, 6, 9, 17, 18</sup>

Neff,<sup>19</sup> in 1932, reported twin sisters who developed hyperthyroidism at the age of eight and 10 years respectively. Fife<sup>20</sup> has recorded twin brothers who developed the disease at the age of 22 years. Careful search of the literature has not revealed the occurrence of the disease in dissimilar twins.

#### CASE REPORT

This child was first admitted to the University Hospital on November 26, 1940 at the age of four years 11 months. His parents stated that for four weeks there had been nervousness and bulging of the eyes with polyphagia and the passage of three or four soft stools a day. In addition there had been enuresis two to three times nightly.

The child was born full term as one of dissimilar twins. A paternal aunt has a toxic goiter.

Physical examination revealed an overactive, irritable, talkative male child with a frequent brassy cough. The height was 43 inches and the weight 40 pounds. There was a marked degree of symmetrical exophthalmos with a pronounced lid lag and no wrinkling of the forehead on upward deviation of the eyes. He was unable completely to close his eyes. The skin was warm and moist with no eruptions. The thyroid

gland was diffusely enlarged and firm with a smooth, regular surface. A loud systolic bruit was heard over the entire gland, and the lower border of the gland could not be felt beneath the manubrium sternum. There was pronounced tremor of the outstretched hands and the tongue. There were enlarged, non-tender, discrete cervical, axillary and inguinal lymph nodes. The heart was normal in size and position, and the apex impulse was forceful with soft systolic mitral and aortic murmurs. The pulse rate was 122 per minute and the blood pressure 162 mm. Hg systolic and 40 mm. diastolic. The remainder of the examination was negative.

With the exophthalmometer at 92, a reading of 18 was obtained in each eye. There was a leukocytosis of 14,700 with 56 per cent small lymphocytes, and all other laboratory studies were within normal limits. A serum cholesterol was 182 milligrams per cent. A chest roentgenogram showed the heart to be globular in shape but normal

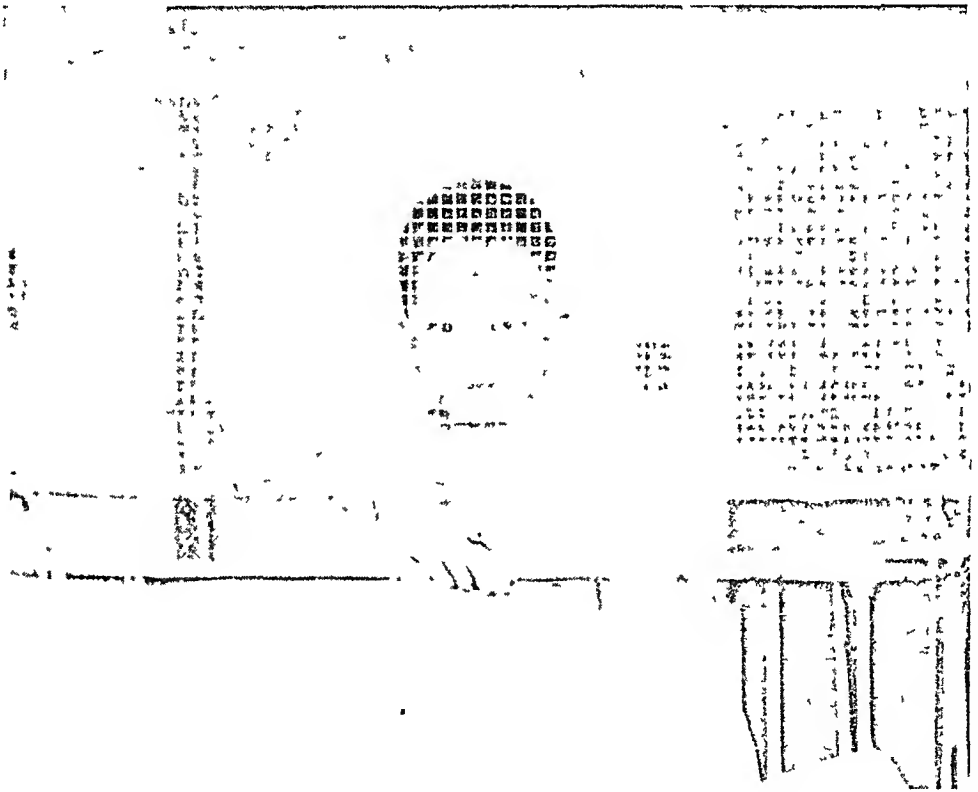


FIG. 1.

in size. There was no evidence of substernal thyroid, but there was an indefinite shadow suggesting a persistent thymus gland. Films of the extremities showed normal ossification, and the sella turcica was normal. An electrocardiogram showed a simple tachycardia with a rate of 107 per minute. There were no other significant changes. A basal metabolism test was attempted with the usual machine and was unsatisfactory.

The patient was placed on Lugol's solution, 10 drops three times a day, a high caloric, high vitamin diet and thiamin chloride, 5 milligrams twice a day. He was extremely restless and irritable, and it was impossible to maintain him as a bed patient. He roamed the hospital wards by day and night and, despite ordinary methods of restraint, was uncontrollable. He entered the premature nursery, seized an infant and after striking its head on the side of a wash basin, placed it under a running hot water

faucet. It was decided that more drastic means of control were required, and he was transferred from the pediatric to the medical service where an appropriate means of confinement had been prepared for him (figure 1). On December 19 a basal metabolic rate of plus 42 per cent was obtained following sedation with 2 grains of seconal.

During the first seven weeks of therapy the activation remained extreme, and the basal metabolic rate rose to plus 72 per cent. He developed a skin rash, nasal discharge and submaxillary gland enlargement, and accordingly the Lugol's solution was decreased to five drops a day. He received a short course of roentgen-ray therapy to the thymic region, and 12 weeks after the institution of iodine therapy the basal



FIG 2

metabolic rate had fallen to plus 35 per cent and he had gained two and one-half pounds. On March 1, 1941 a right subtotal lobectomy with removal of the isthmus was performed under nitrous oxide and ether anesthesia. The 13 grams of tissue removed showed on section a hyperplastic gland with a slight degree of involution.

The postoperative course was complicated by the development of bilateral corneal ulcerations which healed rapidly without demonstrable scarring. Exophthalmometer readings showed a slight decrease in the degree of protrusion (figure 2). Iodine therapy with confinement was continued, and there was a decrease in the degree of activation. He developed uncomplicated rubella, and eight weeks after the first

operation the left lobe was removed, at which time the basal metabolic rate was plus 24 per cent. The pathological picture was identical with that reported for the previous tissue removed, and he was subsequently discharged from the hospital with a basal metabolic rate of plus 5 per cent.

Eleven months after discharge he was readmitted because of lassitude and increasing sensitivity to cold. Physical examination revealed a listless child with a pulse rate of 72 per minute and blood pressure of 104 mm. Hg systolic and 70 mm.

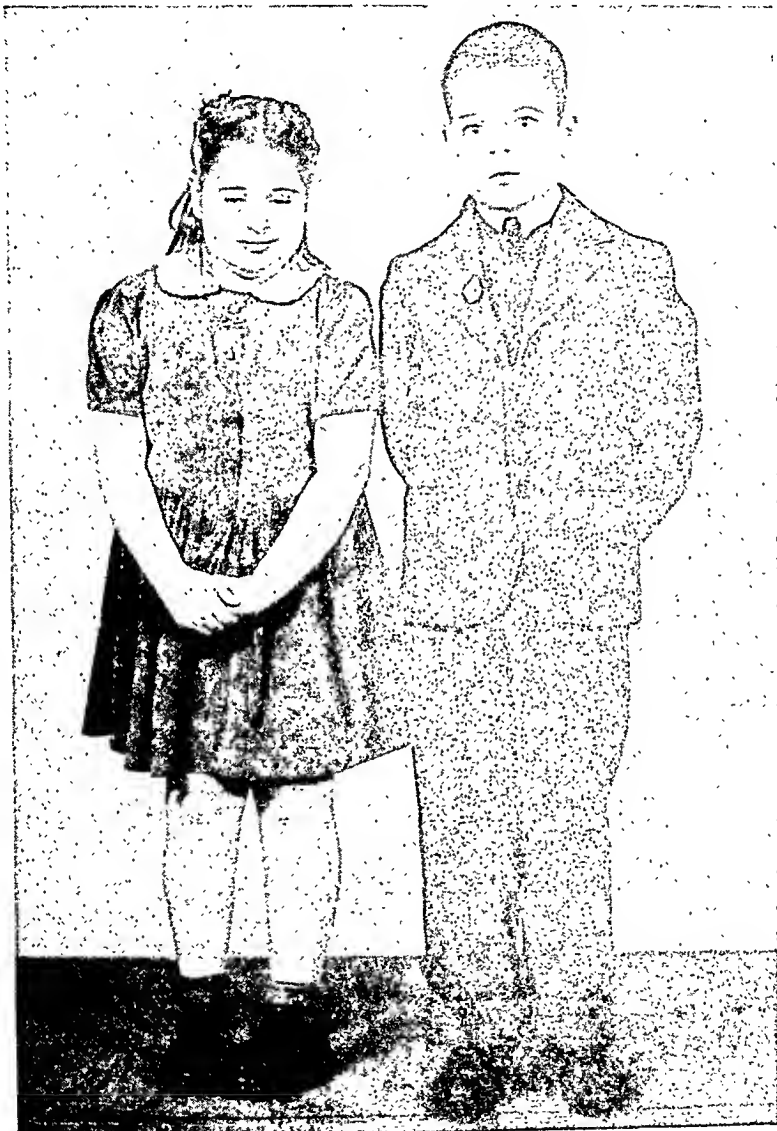


FIG. 3.

diastolic. His height had increased two inches and his weight 12 pounds since discharge. Although there was still a marked degree of exophthalmos, he was now able to close his eyes completely. There was no tremor and the skin was normal.

The basal metabolic rate was minus 36 per cent and the serum cholesterol 292 milligrams per cent. All other studies including an electrocardiogram were within normal limits. After one month of thyroid therapy, the basal metabolic rate had risen to minus 6 per cent, and there were no signs or symptoms of hypothyroidism.



Since discharge from the hospital, he has been maintained on  $\frac{1}{2}$  grain of thyroid daily and has developed as a normal child in all respects. At the age of 10 years he is in the fourth grade of school and has made satisfactory progress throughout his school years. He is not unusually emotional or talkative. There is still a moderate degree of exophthalmos which has not changed for three years (figure 3). There is no palpable thyroid tissue, and the heart sounds are soft with a rate on usual activity of 76 per minute and blood pressure of 104 mm. Hg systolic and 66 mm. diastolic. Height, span, lower measurement and weight are normal for his age. Urinary 17 ketosteroids, cholesterol and basal metabolic rate are within normal limits.

On October 10, 1943, the twin sister, age seven years 10 months, was admitted to the hospital. At five and one-half years enlargement of her neck had been noticed, and increased appetite, nervousness and failure to gain weight had soon appeared. Three months before admission her eyes had begun to bulge.

She had been delivered by a breech extraction and since birth had exhibited a spastic paraplegia. Development was slow; she had not talked until the age of three years, and had first walked at five years.

Physical examination revealed a moderate exophthalmos with lid lag, inability to converge, and absence of wrinkling of the forehead. The thyroid gland was symmetrically enlarged, firm and smooth with no bruit. The heart rate was 120 per minute, and there were no murmurs or enlargement. The blood pressure was 134 mm. Hg systolic and 66 mm. diastolic. There was a spastic paresis of the lower extremities. The basal metabolic rate was plus 49 per cent, and an electrocardiogram showed left ventricular strain with slight myocardial abnormality. Serum cholesterol was 191 milligrams per cent, and all other laboratory studies were within normal limits. Roentgenograms of the heart and lungs, long bones, and sella turcica were normal.

She was placed on a high caloric diet and sedated with 1 grain of phenobarbital a day. Shortly thereafter she developed an acute upper respiratory infection, and iodine therapy was, therefore, delayed until November 10, 1943 at which time all respiratory signs and symptoms had disappeared. She received 10 drops of Lugol's solution three times a day, and after 26 days of therapy the basal metabolic rate had fallen to plus 11 per cent, and she showed marked clinical improvement with a weight gain of 11 pounds. On December 16, 1943 a total thyroidectomy was performed under avertin and ether anesthesia. The postoperative course was uneventful, and she was discharged on December 23, 1943.

The pathological report described an intact thyroid gland in which no adenomata were seen. Microscopic examination revealed a hyperplastic gland with a slight degree of involution.

Three months after operation she was seen in the pediatrics dispensary because of increasing languor. Physical examination revealed a pulse rate of 60 per minute and blood pressure of 86 mm. Hg systolic and 48 mm. diastolic with no other stigmata of hypothyroidism. The basal metabolic rate was reported as minus 26 per cent, and she was placed on  $\frac{1}{2}$  grain of thyroid daily with subsequent improvement. However, she was readmitted to the hospital on August 4, 1944, seven and a half months after operation, at which time her parents complained of her fatigability and slowness in action, both mentally and physically. The basal metabolism rate of minus 8 per cent was obtained and the thyroid was increased to 1 grain a day with prompt improvement. Since that time her hypothyroidism has been completely controlled with thyroid. There is no residual exophthalmos and no palpable thyroid tissue. The heart rate on normal activity averages 70 per minute and the blood pressure 94 mm. Hg systolic and 62 mm. diastolic. She has remained moderately overweight and at 10 years of age weighs  $78\frac{1}{4}$  pounds with a height of 129 cm., span 121.5 cm., and lower measurement 66 cm. The urinary excretion of 17 ketosteroids, blood cholesterol and basal metabolic rate are within normal limits.

## SUMMARY

A set of dissimilar twins in whom hyperthyroidism developed at the age of four years 10 months and seven years 10 months is reported. Following iodine therapy, subtotal thyroidectomy in multiple stages was performed in one patient, and a total thyroidectomy in the other. Postoperatively both patients manifested hypothyroidism which has been satisfactorily controlled with desiccated thyroid.

In the male child the degree of activation was extreme, necessitating confinement for the safety of himself and others.

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## CIRRHOSIS OF THE LIVER ASSOCIATED WITH ALCOHOLISM; REPORT OF ACUTE EXACERBATION WITH SERIAL LIVER BIOPSIES \*

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THE pathologic demonstration of the changes occurring during the course of cirrhosis of the liver has, until the recent revival of interest in liver biopsy, depended on the collection of single specimens of series of postmortem examinations or sporadic operations. Only rarely has there been available more than one observation on a given patient. Consequently, a series of liver biopsies obtained during a period of acute activity in a case of cirrhosis of the liver is of sufficient interest to justify reporting this case.

### CASE REPORT

G. W. T., a 42 year old white highway engineer, was admitted to Touro Infirmary on April 2, 1946, with a chief complaint of jaundice. Fifteen years before admission, because of marital difficulties he began to drink from one-half to one pint of whiskey a day. He continued consuming large quantities of whiskey until 1941 when, following several weeks of increased drinking (one-fifth gallon a day), he noticed for the first time that his liver was enlarged. At that time there was dyspnea, nausea and vomiting but neither jaundice nor pain. He was told that he had some type of heart trouble. He discontinued drinking alcoholic beverages from this time until January 1946 and his liver decreased in size considerably but remained somewhat enlarged. Three months before admission to the hospital (January 1946), subsequent to a demand for more alimony from his divorced wife, he again began to consume large amounts of alcohol to the exclusion of eating. Three weeks before admission the liver was again noted to be enlarged and 10 days before admission jaundice was apparent. Three days before we saw him the feet, legs and abdomen began to swell gradually. Vomiting occurred on three occasions during the week before admission. There was nocturia (two times) with a history of dark urine for several days. The skin did not itch. The stools were light but not completely clay colored.

*Physical Examination.* The patient was a moderately obese, chronically ill, middle aged man lying propped up in bed. He was perspiring and moderately dyspneic. The blood pressure was 144 mm. Hg systolic and 74 mm. diastolic in both arms; the pulse rate was 140 beats per minute; the temperature was 100° F.; and the respiratory rate was 28 per minute. The skin, sclerae and mucous membranes were moderately icteric. The fundal vessels showed slight sclerosis. The heart was overactive but not definitely enlarged; the rate was 140 beats a minute and there was a gallop rhythm. Bilateral moist râles were heard posteriorly at the pulmonary bases. The diaphragms were high and the abdomen was moderately distended. There was an increase in collateral venous circulation, and shifting dullness in the flanks and a fluid wave were easily elicited. The liver was down 20 cm. below the right costal margin extending about 3 to 4 cm. below the umbilicus. The notch was easily palpable, and there seemed to be a large nodule immediately to the right of the notch. The spleen was not felt although examination was difficult because of distention and ascites. The feet, legs, abdominal wall and sacral region were considerably swollen.

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**Laboratory Studies.** On admission the venous pressure was 226 mm. of water in the right arm with rise to 270 on abdominal pressure. Arm to tongue circulation time was 10 seconds.

The urine was acid with a specific gravity of 1.005. The reactions for albumin and sugar were negative and positive for bile and urobilinogen. There were occasional finely granular casts and several epithelial cells on microscopic examination. The reaction to the serologic test for syphilis was negative. Bleeding time was three minutes and coagulation time two minutes. The hemoglobin was 83 per cent, red blood cell count 4,600,000, white blood cell count 18,800 (figure 1), neutrophils 92

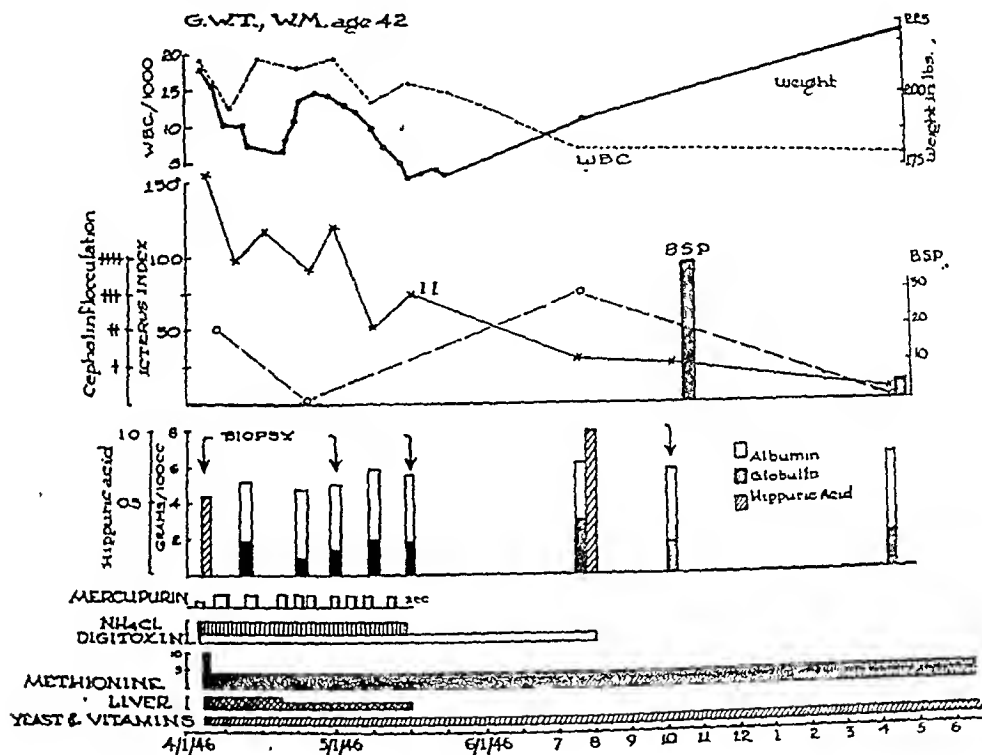


FIG. 1. Graphic representation of clinical course of G. W. T. from April 2, 1946 to June 1, 1947.

WBC—white blood count in thousands. O---O—cephalin flocculation. BSP—Brom-sulfalein retention test 5 mg./kg. 45 min. spec. Mercupurin—in 2 c.c. doses except the first. NH<sub>4</sub>Cl—ammonium chloride 6 gm. per day. Digitoxin—1.2 mg. first day then 0.2 mg. per day. Methionine—10 gm. intravenously first day then 4 gm. day orally. Brewer's yeast—0.5 oz. three times day. Vitamins—1 Squibb therapeutic capsule a day. Hippuric acid—1.75 mg. sodium benzoate intravenously.

per cent, lymphocytes 8 per cent, prothrombin time 90 per cent of normal, cephalin flocculation 2 plus in 24 hours, non-protein nitrogen 27.1 mg. per cent, CO<sub>2</sub> combining power 50.4 mg. per cent, dextrose 97.5 mg. per cent, and icterus index 160.

An electrocardiogram showed definite evidence of myocardial disease. There was depression of the T-waves and ST segments in L I, II and CF<sub>5</sub>. T<sub>3</sub> was inverted. A roentgenogram of the chest revealed cardiac enlargement with a transverse diameter of 15.8 cm., as well as chronic passive congestion of the pulmonary fields.

The patient was immediately digitalized with 1.2 mg. of digitoxin, and he was given 1 c.c. of mercupurin intravenously.

Liver biopsy done with a Roth-Turkel needle<sup>1</sup> on April 5, 1946 revealed indistinct lobules, the cell cords showing extensive large and small fat droplets, cellular de-

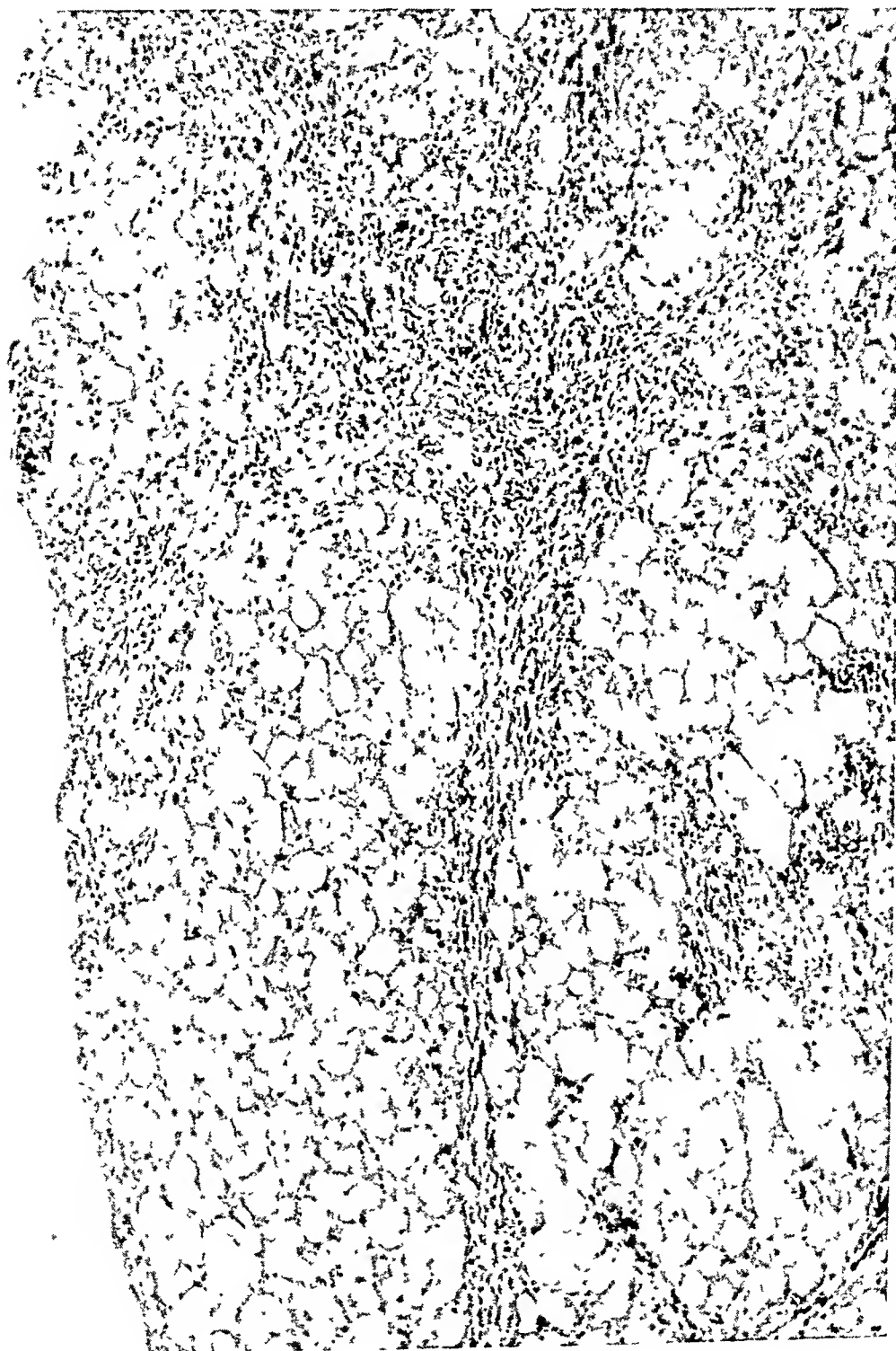


Fig. 2a. Photomicrograph (April 4, 1946) showing perilobular and intralobular fibrosis with diffuse fatty change, degeneration and neutrophilic infiltration. Moderate bile duct proliferation can be seen in the portal areas.  $\times 80$ .

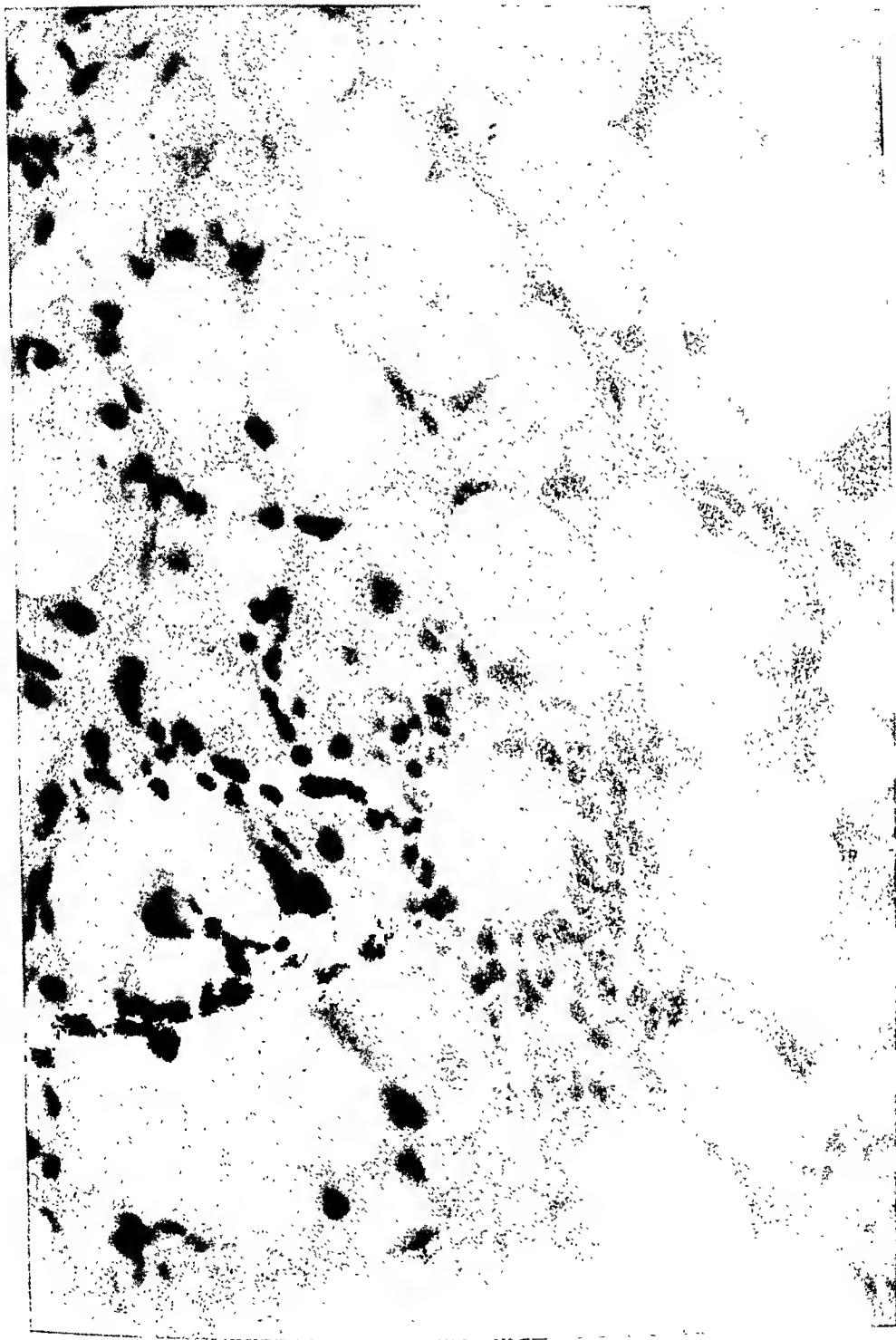


FIG. 2b. Photomicrograph (April 4, 1946) showing intralobular collections of polymorphonuclear leukocytes with cellular degeneration and fatty change.  $\times 400$ .

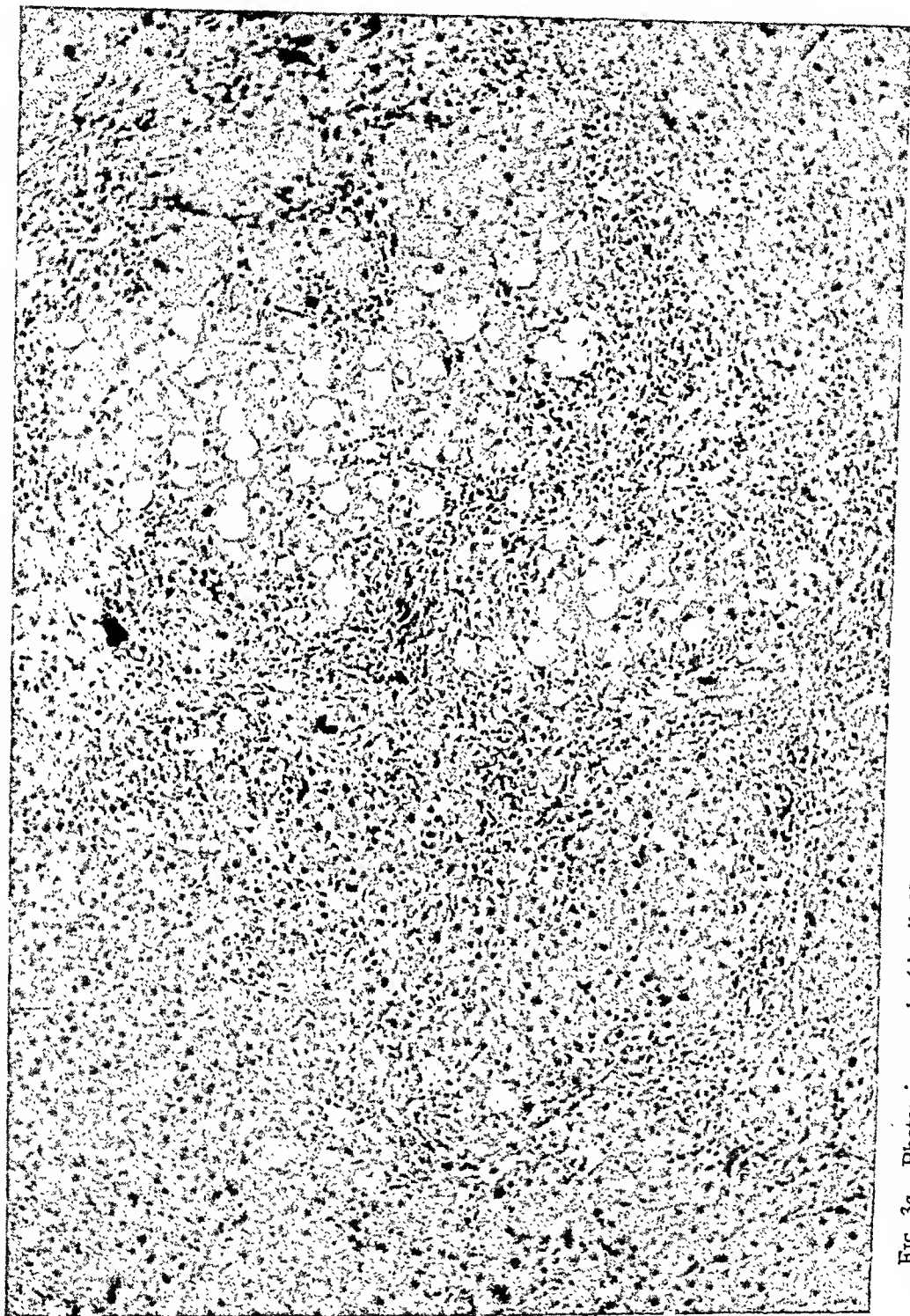


FIG. 3a. Photomicrograph (April 30, 1946) showing decrease in hepatic cellular degeneration and fatty change with increase in glycogen storage. Evidence of regeneration in binucleated liver cells. Neutrophilic infiltration still prominent, though increased numbers of round cells are beginning to appear.  $\times 80$ .



generation and diffuse neutrophilic infiltration (figure 2). Biliary thrombi were not infrequently seen, and there was considerable portal fibrosis with proliferation of biliary radicals. The microscopic diagnosis\* was "portal cirrhosis, severe; fatty degeneration of the liver, severe; acute parenchymatous degeneration with neutrophilic response."

*Hospital Course.* The patient was given methionine‡ (10 gm.) intravenously and started on a diet of carbohydrate (500 grams) and protein (200 grams) with no fat added. Methionine (1 gm.) was given four times a day by mouth, brewer's yeast (0.5 oz.) three times a day, crude liver extract 5 c.c. intramuscularly daily for five days and then three times a week.

On April 8, 1946 the white blood count was 13,050, neutrophils 90 per cent, lymphocytes 7, eosinophiles 3, icterus index 100. On April 9, 1946 the hippuric acid excretion test with 1.77 gm. of sodium benzoate given intravenously yielded 0.535 gm. of hippuric acid in one hour in the urine. On April 11 the total serum protein was 5.17 gm. per 100 c.c., serum albumin 3.3 gm. per 100 c.c., serum globulin 1.87 gm. per 100 c.c. On April 12 the white blood cell count was 19,350, neutrophils 90 per cent, lymphocytes 8, eosinophiles 1, monocytes 1. On April 13 the icterus index was 120. On April 15 the electrocardiogram showed no change from the previous one. On this date the white blood cell count was 17,750, neutrophils 84 per cent, lymphocytes 13, eosinophiles 3, prothrombin time 60 per cent, non-protein nitrogen 27, icterus index 90, total serum protein 4.66 gm. per 100 c.c., serum albumin 3.66 gm. per 100 c.c., serum globulin 1.00 gm. per 100 c.c. On April 16 the prothrombin time was 48 per cent of normal as a consequence of which menadione was started parenterally.

The patient's condition remained essentially the same until April 17, 1946, when 600 c.c. of clear, bile-stained fluid were removed by paracentesis, following which the spleen was felt about 6 cm. below the left costal margin. Mercupurin was given about three times a week and the edema gradually cleared. Venous pressure on April 25, 1946 was 150 mm. of water increasing to 290 on liver pressure with arm-to-tongue circulation time 13 seconds. On April 29, 1946, the white blood cell count was 18,450, neutrophils 87 per cent, lymphocytes 8, eosinophiles 2, monocytes 1, prothrombin 78 per cent, non-protein nitrogen 27, icterus index 120, total serum protein 4.99 gm. per 100 c.c., serum albumin 3.30 gm. per 100 c.c., serum globulin 1.49 gm. per 100 c.c.

Biopsy repeated on April 30, 1946 (figure 3) revealed accentuation of all the features seen in the first biopsy with the exception of fatty metamorphosis which was moderately reduced in this specimen. From the appearance of the biopsy, the liver reserve was considerably diminished. The diagnosis was "portal cirrhosis, severe; fatty degeneration of liver, severe; acute parenchymatous degeneration with neutrophilic response." The glycogen storage in this specimen was much more in evidence than in the previous one and the neutrophilic infiltration was, in general, lessening. Eosinophilic and round cell infiltration was beginning to be noticeable. On May 6 the white blood cell count was 13,700, prothrombin time 90 per cent, non-protein nitrogen 26 mg. per cent, icterus index 50, total serum protein 5.85 gm. per 100 c.c., serum albumin 3.85 gm. per 100 c.c., serum globulin 2.00 gm. per 100 c.c. On May 13 the white blood cell count was 16,350, the prothrombin time was 90 per cent, total serum protein 5.48 gm. per 100 c.c., serum albumin 3.68 gm. per 100 c.c., serum globulin 1.80 gm. per 100 c.c. The venous pressure was 110 mm. of water increasing to 118 mm. of water on liver pressure with circulation time 14 seconds.

A roentgenogram of the chest showed clear lungs and a normal heart measuring 13.1 cm. (2.7 cm. decrease). The electrocardiogram showed definite improvement in that the T-waves were normal and the ST segments were only slightly depressed.

\* Made by Dr. S. Harvey Colvin, Touro Infirmary Pathologist, for whose advice and suggestions we are extremely grateful.

‡ Kindly made available by Wyeth, Inc.



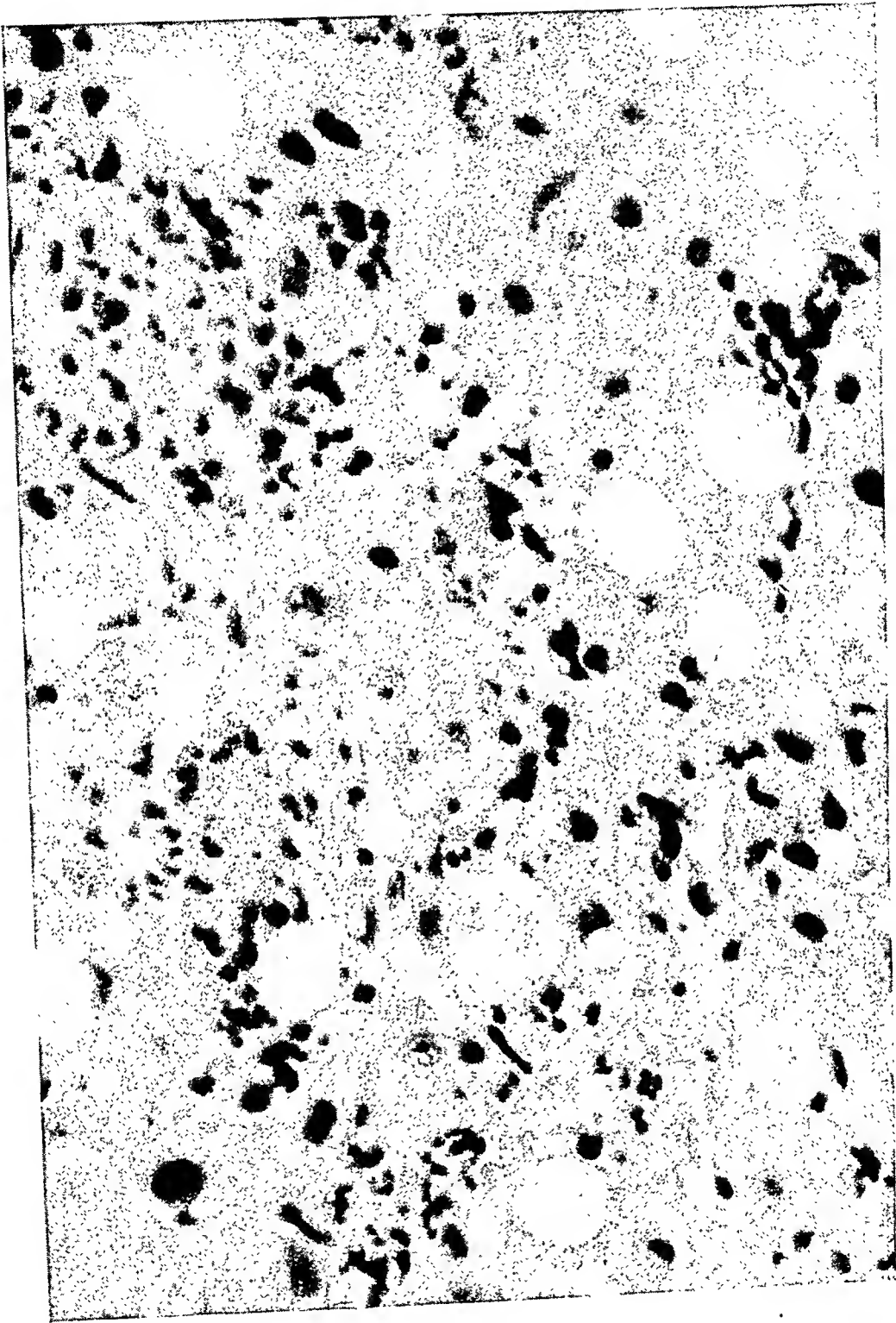


FIG. 3b. Photomicrograph showing increased glycogen storage in liver cells with moderate fatty change and marked neutrophilic infiltration. Note smudges of hyaline degeneration of liver cells in these areas.  $\times 400$ .

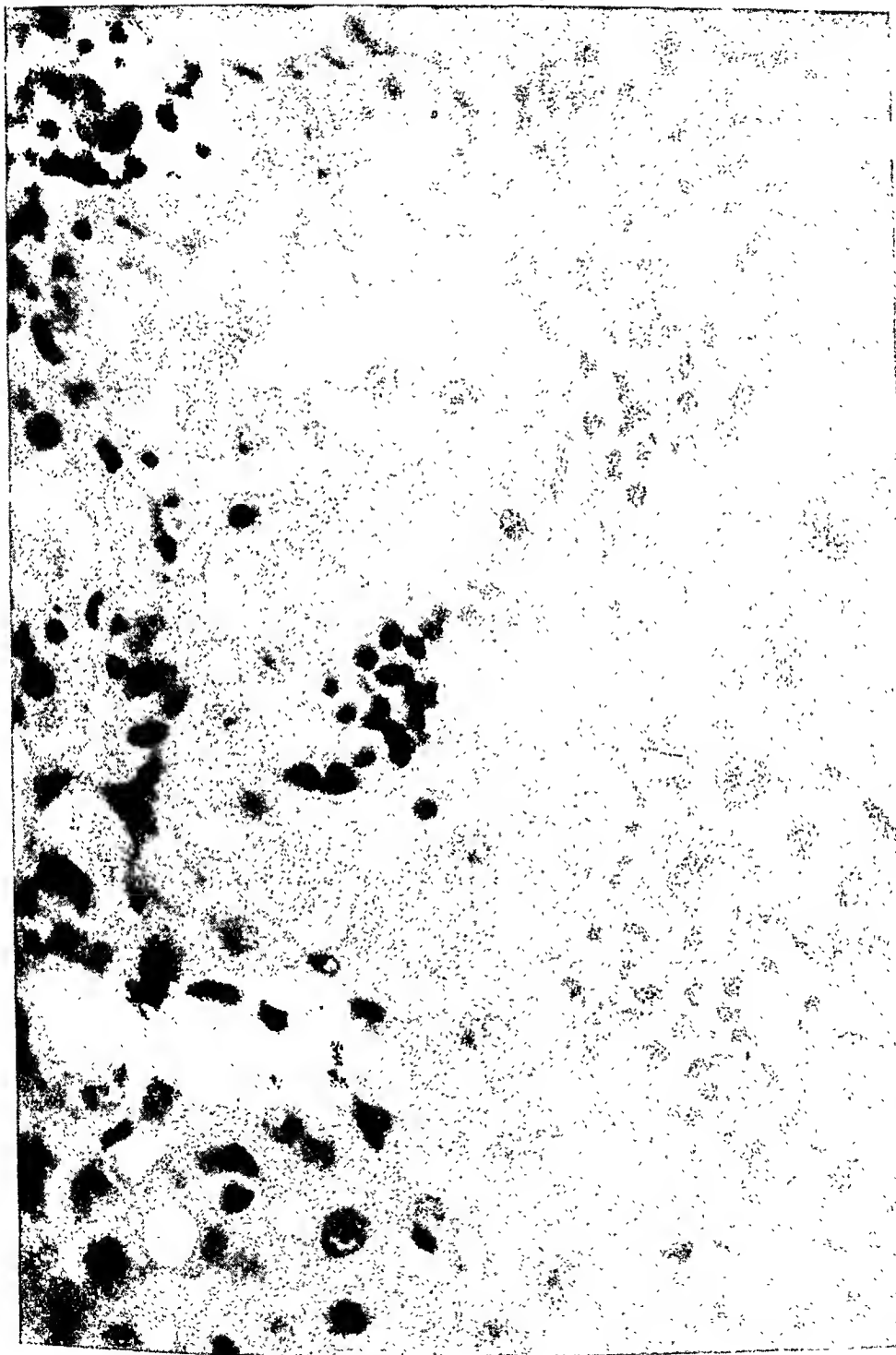


FIG. 3c. Photomicrograph showing a collection of round cells in intralobular situation.  $\times 400$ .

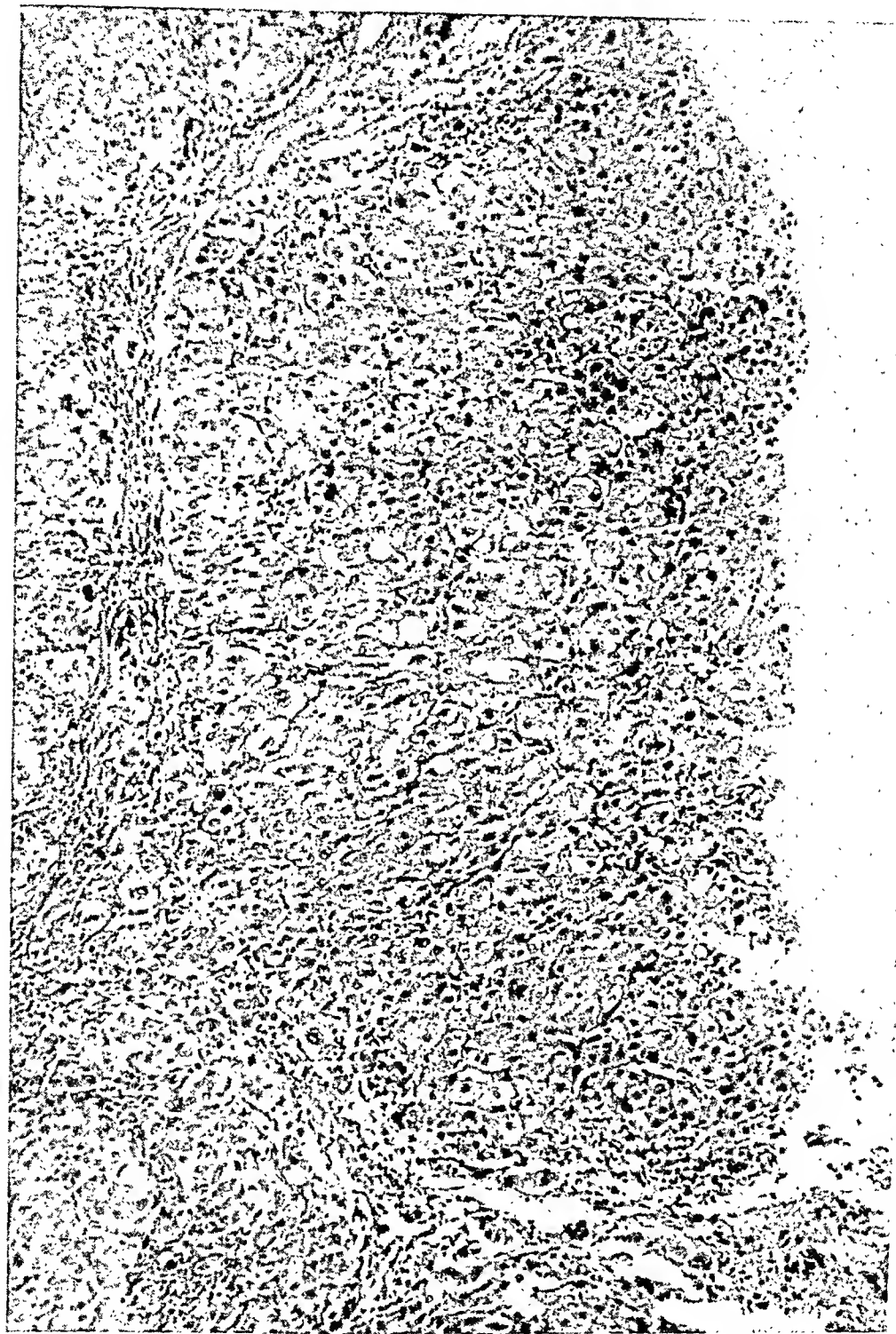


Fig. 4a. Photomicrograph (May 14, 1946) showing little remaining fatty change and moderate cellular infiltration chiefly of round cell type. Marked glycogen storage is seen.  $\times 80$ .

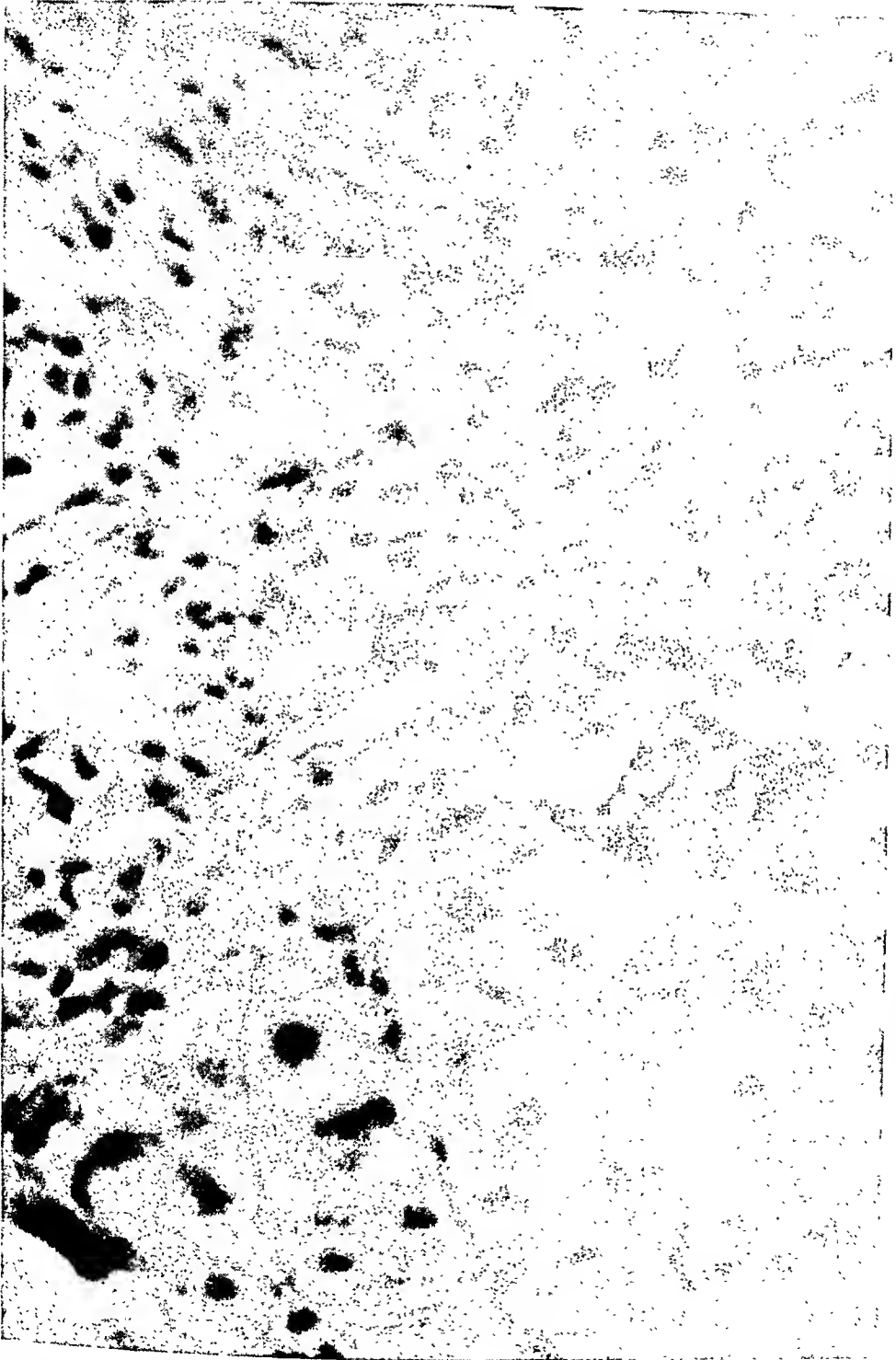


FIG. 4b. Photomicrograph showing remaining parenchymal and fibrous tissue cellular infiltrate chiefly round cell in nature.  
× 400.

The congestive failure had completely subsided by May 13, 1946, and the patient was feeling a great deal better.

In the third biopsy on May 14, 1946 (figure 4) microscopic examination revealed that the lobules were made up primarily of large glycogen-filled granular appearing cell cords surrounded by moderate amounts of connective tissue infiltrated with round cells. Several lobules contained foci of infiltration with large fat droplets and focal collection of neutrophils. Biliary thrombi were occasionally noted as in the previous biopsies. The greater part of the cellular infiltration, however, was made up of round cells. This biopsy suggested that the liver reserve, though still considerably diminished, was better than in previous biopsies. The diagnosis was severe portal cirrhosis, slight fatty degeneration of the liver, and acute parenchymatous degeneration with mild neutrophilic response. There was also considerable evidence of regeneration both of bile ducts and hepatic parenchyma.

The patient adhered rigidly to his diet though he had a rather severe degree of anorexia. He had a low grade fever (99.5° F.) during most of his hospital stay.

The patient was discharged from the hospital on May 17, 1946. He continued his therapeutic regimen at home with minimal physical activity, methionine, brewer's yeast, vitamins\* and diet as before. He returned on July 17, 1946 looking and feeling well. His weight had increased from 175 to 190 pounds, which represented largely muscle. There was no visible icterus. The blood pressure was 140 mm. Hg systolic and 80 mm. diastolic in the right arm in the supine position. The chest was clear, the heart not enlarged, and the rate 90 per minute, with regular sinus rhythm. Soft systolic, pulmonic and mitral murmurs were heard. The abdomen was relaxed, the liver was down only 3 cm. below the right costal margin and the spleen 4 to 5 cm. There was minimal edema of the ankles.

Laboratory studies at this time revealed the following: total serum protein 6.2 gm. per 100 c.c. with albumin 3.2 gm. per 100 c.c. and globulin 3.0 gm. per 100 c.c., non-protein nitrogen 20 mg. per cent, bilirubin 2.8 mg. per cent, hippuric acid excretion 1.0 gm., sedimentation rate 3 mm. per hour, red blood cell count 4,100,000, hemoglobin 80.5 per cent, white blood cell count 7,500, polymorphonuclears 64 per cent, lymphocytes 27, monocytes 5 and eosinophiles 4.

The patient was again discharged with instructions to follow the previous regimen. He returned October 5, 1946 feeling well and working full time with an hour's rest in the middle of the day. There was absolutely no evidence of heart disease, ascites or edema. Blood pressure was 130 mm. Hg systolic and 75 mm. diastolic in the right arm. The chest was clear. The heart was not enlarged, the rate 80 per minute, rhythm regular sinus with an occasional ectopic beat and no murmur. The abdomen was relaxed. The liver, which was down 2 cm. below the right costal margin, was firm, smooth and nontender. It descended to 6 cm. on deep inspiration and the spleen descended only 2 cm.

Another liver biopsy was done on October 7, 1946 (figure 5). Sections revealed numerous islands of glycogen-filled cell cords surrounded by considerable amounts of fibrous connective tissue. There was moderate biliary radical proliferation. The diagnosis was portal cirrhosis of the liver. The glycogen content was notably increased and the fat was absent. Cellular infiltration had completely disappeared and there was no evidence of degeneration at this time.

Laboratory studies revealed total serum protein 5.8 gm. per 100 c.c., serum albumin 4.1 gm. per 100 c.c., serum globulin 1.7 gm. per 100 c.c., non-protein nitrogen 22 mg. per cent, bilirubin 2.64 mg. per cent, bromsulphalein excretion test, 37 per cent retention at 60 minutes, sedimentation rate 1 mm. per hour, red blood cell count 4,480,000, hemoglobin 14.5 gm. per cent, white blood cell count 7,350, neutrophils 47 per cent, lymphocytes 37, monocytes 6, eosinophiles 8, basophiles 2, cephalin floccula-

\* Squibb therapeutic.



FIG. 5a. Photomicrograph (October 7, 1946) showing complete absence of fatty change and cellular infiltration. There is marked glycogen storage and still some evidence of regeneration of liver tissue.  $\times 80$ .

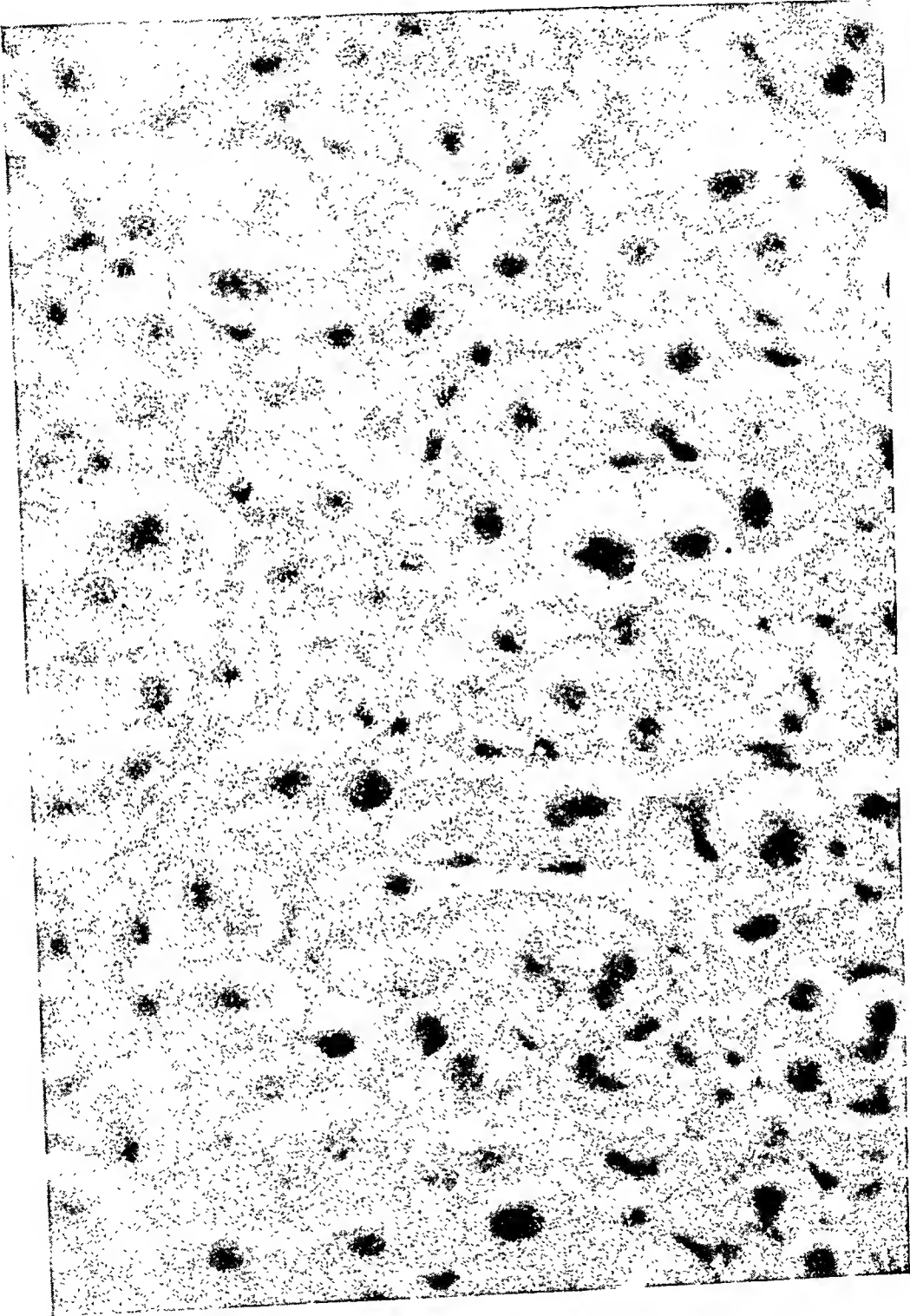


FIG. 5b. Photomicrograph showing glycogen filled liver cells—several with two nuclei and no cellular infiltration.  $\times 400$ .



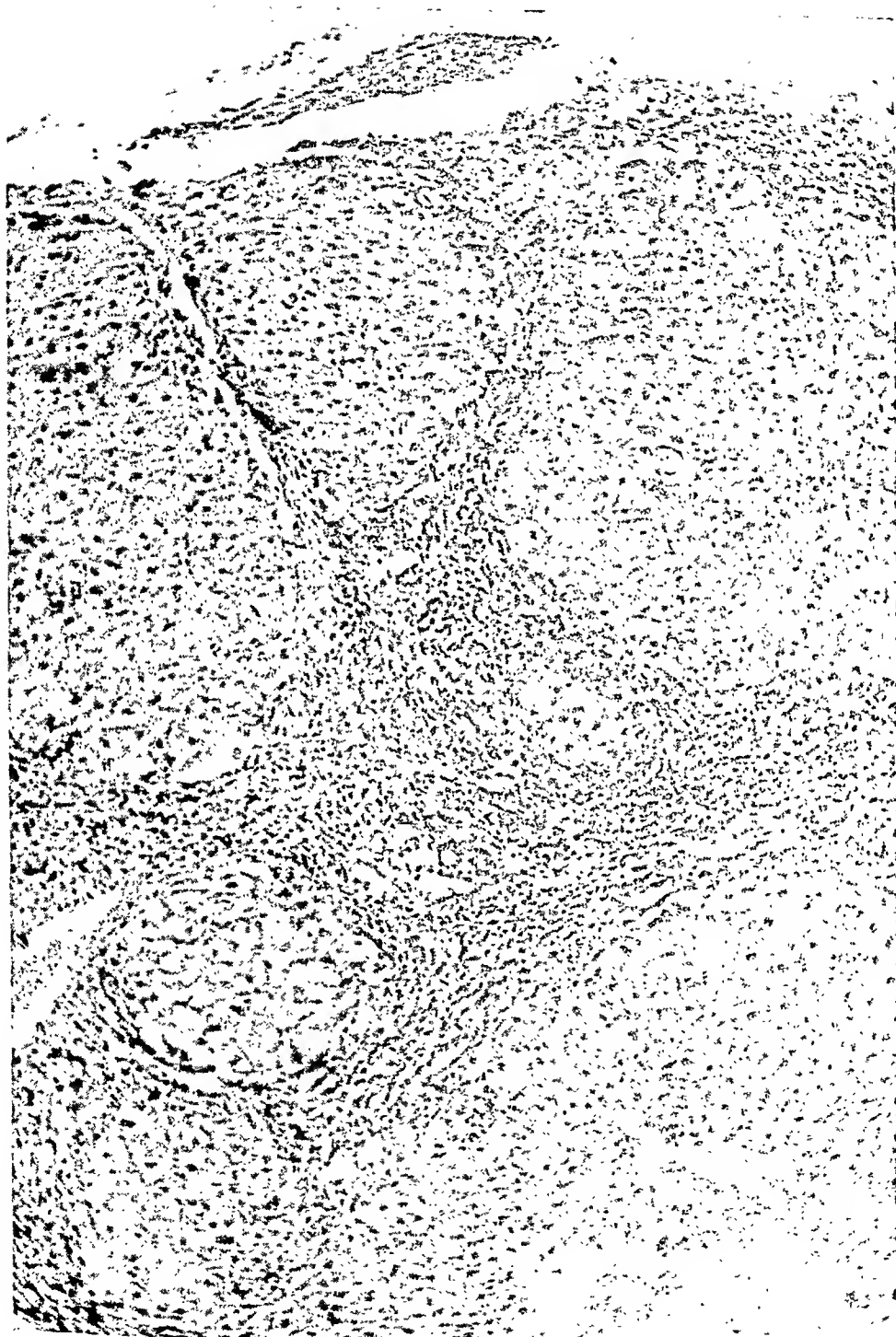


FIG. 5c. Photomicrograph showing another area from the same slide to illustrate variation in fibrosis in different areas of the liver.  $\times 80$ .



tion test 3 plus, prothrombin time 116 per cent. The reaction to the test for bile in the urine was negative, for urobilinogen positive in dilution of 1:20.

The patient was again discharged; he was permitted to work full time and told to continue with his diet, methionine and vitamins. He returned on April 12, 1947 feeling perfectly well, working full time but still taking no strenuous exercise. He weighed 222 pounds at this time. The blood pressure in the right arm was 140 mm. Hg systolic and 85 mm. diastolic. The fundi were normal; there was no trace of icterus; the chest was clear and the heart normal. The abdomen showed no evidence of increased collateral circulation; the liver still descended 5 to 6 cm. below the right costal margin on deep inspiration and was firm and nontender; the spleen was about half its size on the previous visit, coming down 1 to 2 cm. on deep inspiration. There was no edema.

Laboratory studies at this time were as follows: red blood cell count 5,200,000, hemoglobin 94 per cent, while blood cell count 6,900, neutrophils 47 per cent, lymphocytes 52, eosinophile 1, urine urobilinogen excretion 0.96 Ehrlich unit for two hour period, total serum protein 6.4 gm. per 100 c.c., serum albumin 4.3 gm. per 100 c.c., serum globulin 2.1 gm. per 100 c.c., non-protein nitrogen 24 mg. per cent, bilirubin 1.09 mg. per cent, bromsulfalein 5 per cent retention (at 45 minutes); the cephalin flocculation test yielded negative results. The patient had had absolutely no alcohol since his admission to the hospital April 2, 1946.

### DISCUSSION

The etiology of the cirrhosis in this case seems clearly related to a combination of dietary deficiency and inordinate use of alcoholic beverages. There was no history of blood transfusion, plasma infusion, vaccination, antisiphilitic therapy or other exposure to the virus of hepatitis or chemical hepatotoxin, and no evidence of biliary obstruction. The clinical course of the episode is shown graphically in figure 1. Of particular interest are the presence of persistent, severe, congestive heart failure with electrocardiographic changes which cleared completely as the hepatic disease regressed, close agreement between the fluctuations in icterus index and white blood cell count, a good response to prolonged hyperalimentation, the administration of methionine, brewer's yeast, liver extract and supplementary vitamins, and the laboratory evidences of prolonged hepatic dysfunction after clinical improvement. The low initial value of the cephalin flocculation test and its subsequent increase after other evidences of activity were subsiding is difficult to explain. From the chart it may be seen that there was fairly good inverse correlation with the albumin/globulin ratio.

The presence of congestive heart failure in association with cirrhosis of the liver and ascites has been clinically recognized for many years.<sup>2, 2a</sup> The actual mechanism in the case just described is questionable. The absence of hypertension and valvular defects, and the presence of transient electrocardiographic changes, gain in weight and normal pulse pressure rule out the common causes of heart disease and leave for consideration toxic myocarditis and heart failure due to thiamine deficiency. The fact that there was no concomitant evidence of severe vitamin deficiency mediates against the diagnosis of beriberi heart. The reversible electrocardiographic changes, the roentgenologic decrease in the size of the heart, and the disappearance of congestive failure with control of the hepatic dysfunction favor interpretation of myocardial insufficiency as secondary to the hepatic disease. The pronounced hepatomegaly and ascites were probably related to the combination of hepatic difficulty and cardiac insufficiency whereas the change in size of the liver was related to the reestablishment of myocardial

competency as well as to the disappearance of fatty infiltration and inflammatory reaction. Persistent leukocytosis and low grade fever in association with fatty liver and "alcoholic cirrhosis" have been mentioned by Keefer and Fries,<sup>3</sup> Hall and Morgan,<sup>4</sup> and Davis,<sup>2, 2a</sup> though the cause is not clear. In the present case there was good agreement between peripheral leukocytosis and neutrophilic response in the liver.

Microscopically, of particular interest in the initial biopsy is the severe degree of fatty change, liver cell degeneration and pronounced generalized polymorphonuclear leukocytic infiltration throughout the lobules as well as in the periportal connective tissue (figure 2). Fibrous tissue is present in moderate amount though less noticeable because of the considerable crowding of the fat. Bile duct regeneration and biliary thrombi are present though not particularly noticeable in the first biopsy specimen. Fatty change in the liver is well known in cirrhosis and was first noted by Addison.<sup>5</sup> It has been repeatedly mentioned as the cause of "alcoholic cirrhosis."<sup>3, 4, 6, 7</sup> Discussion of the validity of this contention is not pertinent at this time.

Although the polymorphonuclear leukocytic infiltration has been described previously,<sup>1, 4, 7, 8, 9, 10</sup> extensive diffuse infiltration is apparently not common and there has been relatively little emphasis on its occurrence in the past few years. The significance of neutrophilic infiltration is obscure. It has been suggested that such change is in response to ascending bacterial or chemical cholangitis, but in such an instance the change should be localized to the peribiliary areas and this was not the case. Neutrophilic response to cellular degeneration is a well known pathologic phenomenon, but again the specific reason for its appearance in some situations and absence in others is not clear. For example, in the severe cellular degeneration of epidemic hepatitis,<sup>11, 12, 13</sup> acute yellow atrophy,<sup>14</sup> yellow fever<sup>15</sup> and related conditions, neutrophilic infiltration, though present in some instances, is not great and the predominating cells are usually round cells. It is believed that the presence of such diffuse neutrophilic infiltration may have diagnostic significance in acute degenerative change associated with alcoholism and malnutrition. It is apparently not associated with the fatty infiltration of the liver in pellagra.<sup>16</sup> The specific factor responsible remains to be identified.

Subsequent biopsies in the case reported showed gradual disappearance first of the fatty degeneration with replacement by glycogen, and later disappearance of the polymorphonuclear leukocytes and replacement by round cells, with accentuation of the biliary radicals and increase in perilobular and intralobular fibrosis. This is probably a relative rather than an absolute change depending on the disappearance of fatty infiltration. In the last biopsy there remained only the picture of quiescent cirrhosis. It is, of course, impossible to assess accurately the place of methionine in the therapeutic response of this patient because of the lack of control observations. The clinical impression is, however, that it was of considerable value. Of undoubted benefit was the determined coöperation of the patient in eating all his diet during the whole course of illness.

#### SUMMARY

We have presented a case of cirrhosis of the liver showing an acute exacerbation associated with alcoholism with serial liver biopsies. The series shows

resolution of the severe fatty degeneration and polymorphonuclear infiltration over a period of six months closely paralleling the clinical and laboratory evidences of improvement. Remarkable features included the presence of severe congestive heart failure which disappeared spontaneously with the resolution of the hepatic lesions, low grade fever, leukocytosis, and polymorphonuclear leukocytic infiltration of the liver which also resolved. It is noteworthy that the result of the cephalin cholesterol flocculation test did not follow closely the microscopic and other laboratory evidence of hepatic damage other than the albumin/globulin ratio.

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### RELAPSING FEBRILE NODULAR NONSUPPURATIVE PANNICULITIS: REPORT OF CASE TREATED WITH PENICILLIN \*

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RELAPSING febrile nodular nonsuppurative panniculitis (Weber-Christian's disease) is a rare clinical syndrome which was first described by Pfeiffer<sup>1</sup> in

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1892. Subsequent reports, including one by Weber<sup>2</sup> who added the word febrile to the name, brought the number of cases known at present to 29.

As the name implies, this is a chronic recurrent condition, characterized by attacks of fever associated with nonsuppurating nodules in the subcutaneous fatty tissue. The most common localization is in the lower extremities, and of the 29 cases reported in the literature, 24 have been found in women and only five in men.

The condition occurs in repeated attacks, each of which may last up to several months with spontaneous remissions. There is usually generalized malaise of varying degree. Only one case with a fatal outcome has been reported. The nodules, which are the characteristic feature of this syndrome, vary in size from 0.5 cm. to 5 cm. in diameter. They are usually tender, and the overlying skin has a blue, livid discoloration and shows a definite depression when the nodules undergo involution.

The etiology of relapsing febrile nodular nonsuppurative panniculitis is unknown. However, most observers agree that the halogens (bromides, chlorides, and iodides) may be of etiological significance. In the majority of cases there is definite history of halogen ingestion, and Rosenberg and Cohen<sup>3</sup> cite a case in which they were able to precipitate a recurrence by giving the patient bromides and chlorides.

No specific treatment is known and therapy has been merely symptomatic. Arnold<sup>4</sup> reports a case which responded favorably to sulfapyridine, whereas other observers agree that the sulfonamides are of no benefit. We have not found any reports of cases in which penicillin was used.

In view of the rarity of the condition and the lack of knowledge of its etiology and therapy, we believe that the report of an additional case is justified, particularly since this appears to be the first case treated with penicillin.

#### CASE REPORT

*History.* The patient, a white female, 35 years of age, was admitted to the hospital on September 17, 1946, complaining of hoarseness, sore throat, and lumps in the right calf below the knee.

She had first become ill in January, 1945, when she began feeling tired and noticed pain under the right shoulder blade. She became hoarse and had noticed intermittent hoarseness since that time. In September 1945 she developed fever and headache, and her face became very swollen. These symptoms subsided, but in July 1946 the swelling of the face and the headache recurred, and she developed a sore throat. She had one chill at the time. She then developed several nodules in her right calf. These were not painful, but they burned and caused what she called a "creepy feeling." She had lost 14 pounds in weight during a period of a few months prior to admission, and she had developed several ulcers in her mouth. These ulcers healed but recurred in a few days. Two weeks prior to admission the outer angle of her right eye became sore with swelling of both lids.

The patient stated that she worked as a clerk in a drug store and that she had been taking a great deal of medicine. When asked to write down the drugs she had been taking, she produced the following list from memory: Salts, Vick's Nose Drops, Prothricin Nose Drops, Viburnum plus HVC, Migraine Tablets, P. A. C. Tablets, Mineral Oil, Benadryl Capsules, Kaopectate, a bismuth and magnesium mixture, Sulfathiazole, Aspirin, Cold Capsules, Rexall Kidney Pills, bromoseltzer (about two doses), thyroid tablets, a large blue kidney pill, Menthol Blue, a tonic for

appetite, multiple vitamins, vitamin D pills, and ovarian shots. She had also been using iodized salt for kitchen and table use.

*Physical Examination.* The patient was a white female weighing 118 pounds, who appeared chronically ill. Her blood pressure was 100 mm. Hg systolic and 68 mm. diastolic, temperature 98.2° F., pulse 76, and respirations were 20. There was moderate inflammation of the outer canthus of the right eye with a small fissure,

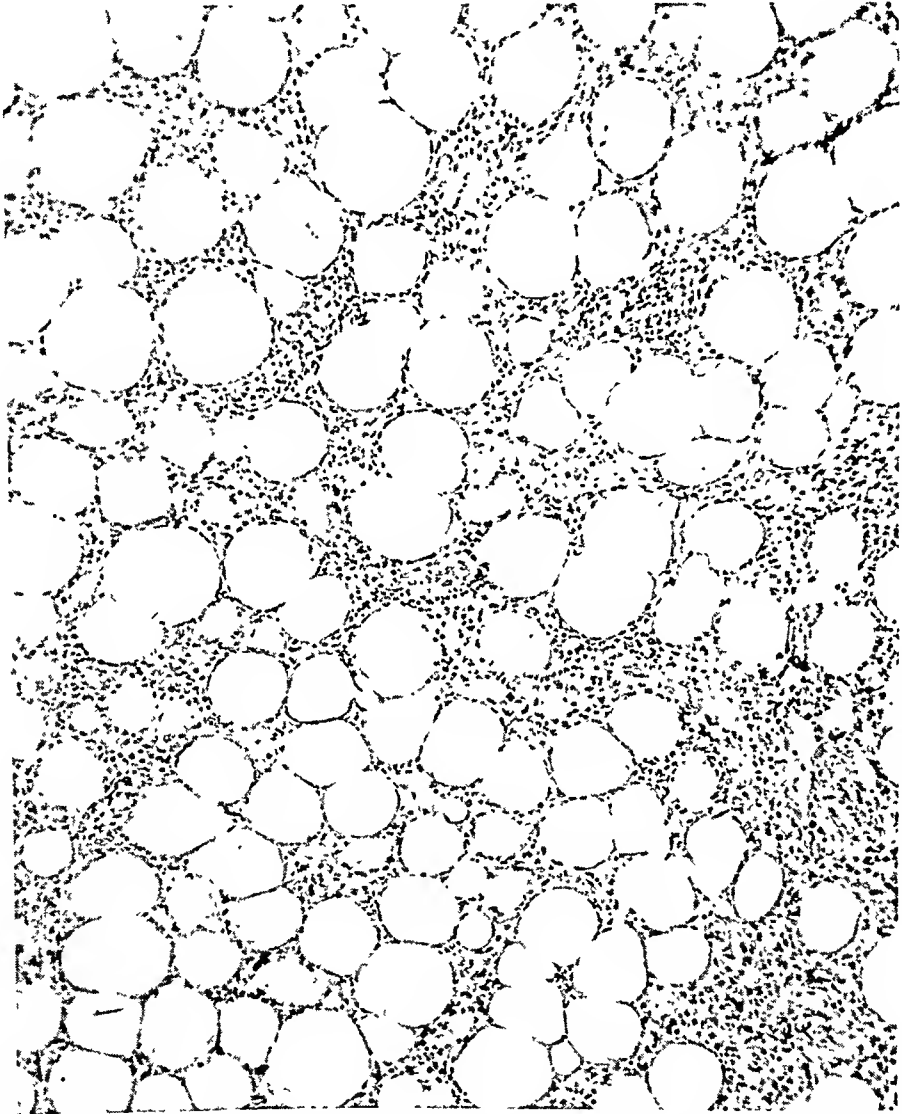


FIG. 1. Low power photomicrograph ( $\times 125$ ) showing the characteristic appearance of the lesion.

and diffuse edema of the eyelids and adjacent tissue. The pharynx showed a vertical ulcer 5 by 3 mm. on the left posterior wall within a red, swollen area. The base of the ulcer was covered with white-yellow mucus. The edges were sharp and slightly indurated but not undermined. The mucous membrane of the larynx was edematous. Several enlarged, submandibular lymph nodes were noted bilaterally.

Numerous discrete, subcutaneous nodules, measuring 5 to 20 mm. in diameter, were found in the right calf in an area extending from a point 5 cm. below the knee

to a point 5 cm. above the Achilles tendon. The nodules were not tender and were freely movable. The overlying skin was livid.

*Laboratory Studies.* Roentgen-ray of the chest was negative. Urinalysis was negative. The red blood cell count was 4,060,000 with a hemoglobin of 12 gm. (Haden-Hausser). The white blood cell count was 5,500. The differential count showed 79 per cent segmented neutrophils, 19 lymphocytes, 1 monocyte, and 1

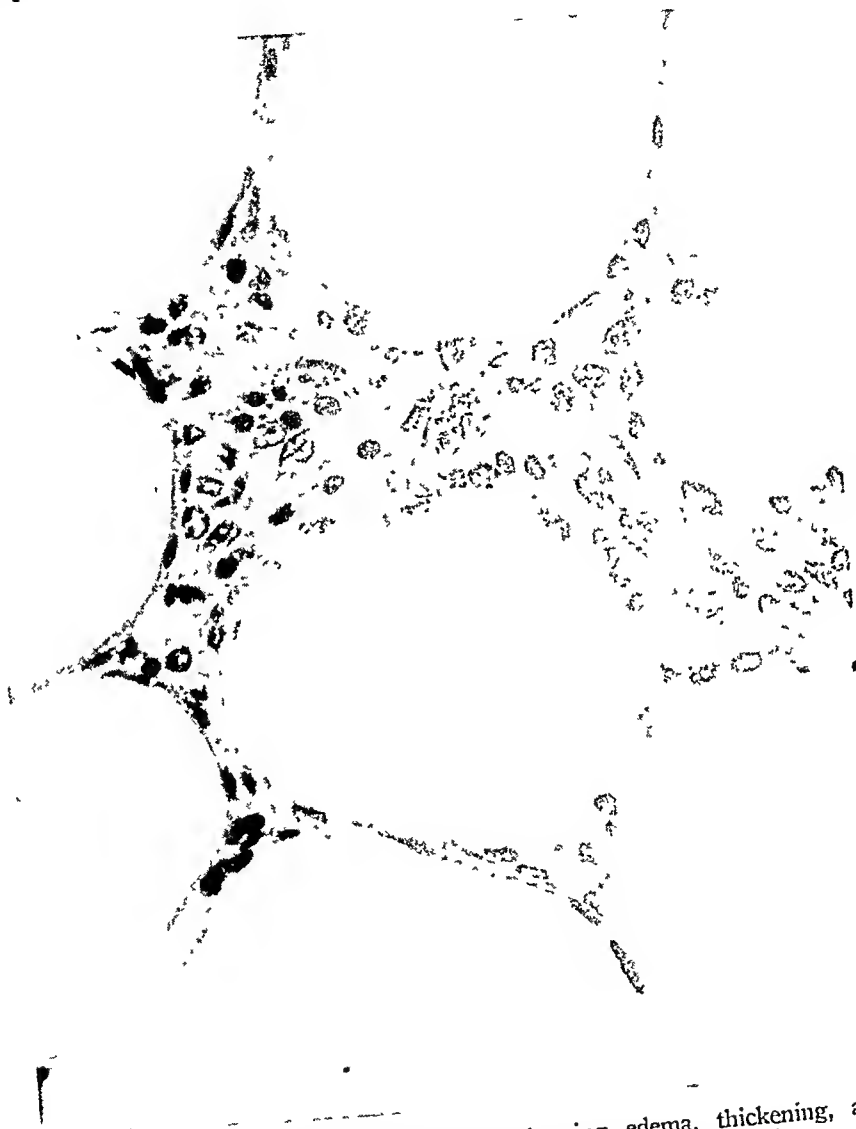


FIG. 2. High power photomicrograph ( $\times 500$ ) showing edema, thickening, and chronic inflammation of the fibrous tissue between the fat cells.

eosinophile. The sedimentation rate was 30 mm. at one hour. One blood culture showed no growth.

Blood Mazzini and Kahn reactions were negative. The spinal fluid Kahn reaction was doubtful, and a trace of globulin was found by the Pandy and Ross-Jones methods. The spinal fluid total protein was 34. The colloidal gold reaction was 1100000000.

A Gram stain from the throat lesion revealed a moderate number of pus cells and gram-positive cocci. No Vincent's organisms were found. Smears for tubercle bacilli and dark field examinations for *Treponema pallidum* were negative.

A tentative diagnosis of infectious granuloma was made, and a biopsy was taken from one of the leg lesions.

*Pathological Report.* Gross examination revealed an elliptical strip of skin measuring 3.5 by 1.4 by 1.0 cm., containing an irregular, wrinkled, slightly elevated, red area in the central portion measuring 1.3 by 1.0 cm. The surface showed no ulceration or scaling. The cut surface showed a few, tiny, red areas in the subcu-

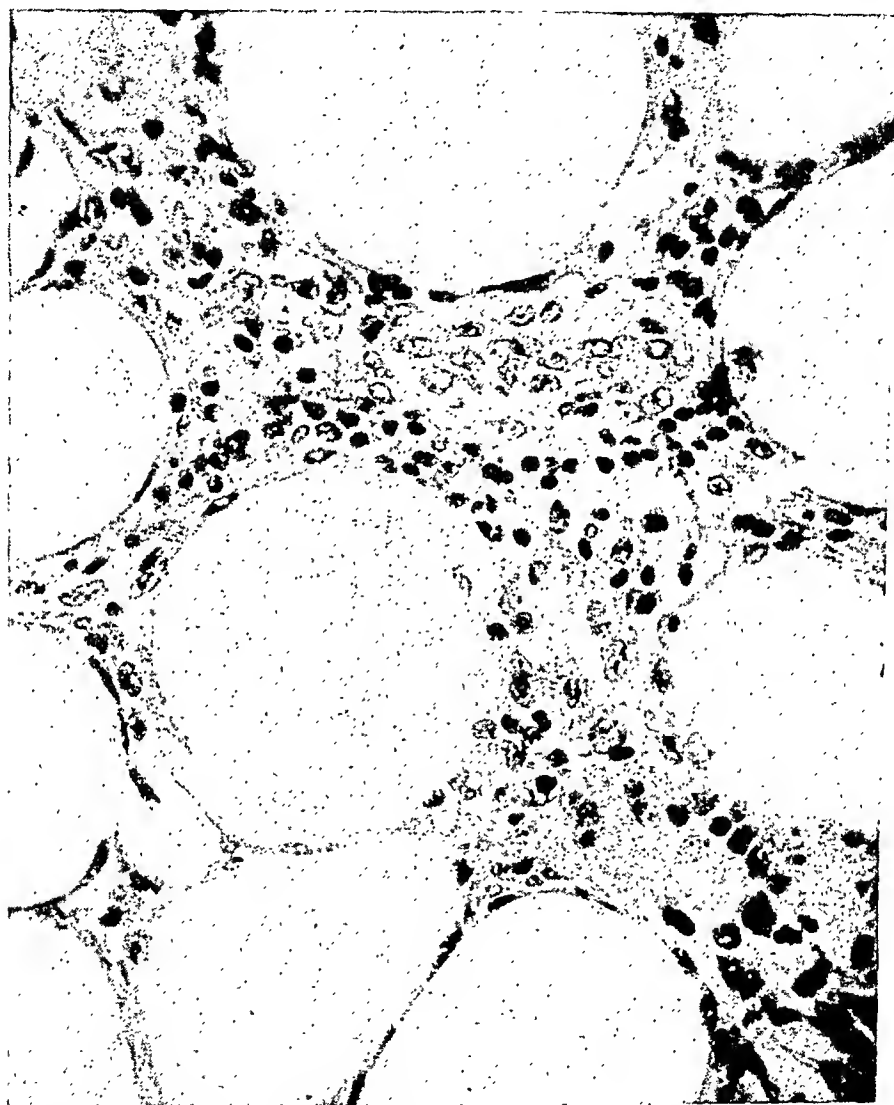


FIG. 3. High power photomicrograph ( $\times 500$ ) showing the granulomatous character of the lesion.

taneous fat. The fatty tissue was firm and nodular, but no well-defined tumor was seen.

Microscopic examination revealed an unusual picture resembling fat necrosis in general appearance. The subcutaneous nodule was made up almost entirely of fatty tissue arranged in poorly outlined lobules separated by fibrous strands. Many fat cells were necrotic, and numerous large monocyctic cells filled with lipoid material were scattered through the tissue. The fibrous tissue between the fat cells was thick and edematous, and it contained a heavy sprinkling of lymphocytes and monocytes and a

few eosinophiles, plasma cells and segmented neutrophils. Some of the tissue cells were large, swollen, and granular, resembling reticular cells. A few mitotic figures were seen in these cells. In a few small areas a granulomatous reaction made up of young fibrous tissue containing a few small collections of chronic inflammatory cells and one or two multinucleated giant cells was noted. There was marked increase in the fibrous tissue surrounding a few of the large blood vessels. A few of the large blood vessels and many of the smaller vessels showed infiltration of lymphocytes and monocytes through the walls and in the perivascular spaces. A few of the smaller vessels showed rather striking fibrinoid degeneration. The overlying epithelium was not remarkable. The corium contained a few collections of chronic inflammatory cells particularly around the small blood vessels. No other changes were noted in the skin.

As most of these pathologic changes have already been described, no attempt is made to show all of them in the accompanying photomicrographs. Low and high power photomicrographs of an area regarded as "representative" of the lesion and a high power photomicrograph of a granulomatous area are shown.

*Course.* The patient was given 40,000 units of penicillin every three hours for seven and one-half days, a total dosage of 2,400,000 units. Her course during several weeks of hospitalization was variable. The condition of the right eye and the throat lesions improved only temporarily. Her temperature ranged between 97.6° F. and 99.6° F. Repeated Mazzini and Kahn reactions were again negative. It was felt that the penicillin had not affected the course of the disease.

In view of the diagnosis, the patient was advised to refrain from all medication and particularly cautioned to avoid iodides and bromides. She was seen again in approximately six weeks after discharge from the hospital, at which time the ulcer in the throat had healed but two smaller ones had appeared in the gum and buccal mucous membrane. The swelling of the eye had almost entirely subsided, and the patient stated that she felt considerably better. The nodules in the leg had almost disappeared. The skin over the lesions was slightly darker than the surrounding skin and showed slight pitting.

### COMMENT

The case is remarkable in several respects. The ulceration of the throat and the blepharitis of the right eye are findings which have not been reported in other cases.

This patient took a great many drugs, several of which contained iodine, and she also used iodized salt. After she discontinued this practice, she had a definite remission of symptoms. We feel that the excessive use of halogens as an etiologic factor, as reported in the literature, may be substantiated by our observations in this case. Penicillin, the use of which, as far as we know, has not been previously reported in this condition, was of no value.

### SUMMARY

A case of relapsing febrile nodular nonsuppurative panniculitis in a 35 year old woman is reported. She had multiple ulcers in her throat and blepharitis of the right eye. There was a definite history of halogen ingestion, and the patient showed marked improvement after discontinuation of all medication. Penicillin therapy (2,400,000 units in seven and one-half days) did not affect the course of the disease.



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4. ARNOLD, H. L., JR.: Nodular nonsuppurative panniculitis (Weber-Christian disease); preliminary report of case controlled by sulfapyridine, *Arch. Dermat. and Syph.*, 1945, li, 94-99.
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## EDITORIAL

### RADIOACTIVE IODINE: PHYSIOLOGICAL AND CLINICAL STUDIES

SINCE 1946 radioactive isotopes of many varieties have become increasingly available to the investigator and clinician as a result of their release for distribution from the atomic energy pile at Oak Ridge, Tennessee. An upsurge of interest in the diagnostic and therapeutic applications of these agents has occurred. Two among the many available elements, radiophosphorus and radioiodine, have already found a distinct place in the modern therapeutic armamentarium. The behavior of these isotopes, among the earliest to be produced artificially, has been extensively studied *in vitro* as well as *in vivo* in animal and human subjects. The data thus obtained offered a basis for further clinical trial and investigation. The purpose of this brief summation is to review some of the pertinent physiological and clinical data which have been accumulated concerning radioactive iodine.

In 1934 Joliot and Curie<sup>1</sup> reported their discovery of artificial radioactivity and in the same year Fermi<sup>2</sup> was able to produce the first radioactive isotope of iodine. Twelve distinct isotopes of radioiodine have been described.<sup>3</sup> These, in common with all radioactive isotopes, behave, in a biological system, in a manner identical with the stable element. They are distinguished, one from the other, by their different atomic weights and by designation of their half-life period. All radioactive elements are unstable and hence as their nuclei emit radiations they undergo decay and transmutation. It can be shown mathematically that the time required for the complete decay and disappearance of a sample of radioactive material approaches infinity, regardless of the rate constant of this decay. In describing radioactive materials, therefore, it has been found convenient to refer to the half-life, the length of time which will elapse before half of the material initially present will have undergone transmutation. Of the twelve isotopes of iodine referred to, only two have been used extensively in biological and clinical investigation. One has an atomic weight of 130 ( $I^{130}$ ) and a half-life of 12.5 hours; the other an atomic weight of 131 ( $I^{131}$ ) and an eight-day half-life. Both are produced by the bombardment of metallic tellurium with deuterons. Radioiodine, like roentgen-rays, emits both beta and gamma rays. The latter are apparently less important for therapeutic purposes. The beta rays on the other hand, having a penetrating power of only a few millimeters will exert their maximum effect only over a small area when, as in the case of the thyroid, they are concentrated within the follicles. Extensive clinical application of a radioactive isotope is obviously distinctly related to its half-life period. Earlier studies with  $I^{130}$  were possible only

<sup>1</sup> JOLIOT, F., and CURIE, I.: Artificial production of a new kind of radio-element, *Nature*, 1934, cxxxiii, 201.

<sup>2</sup> FERMI, E.: Radioactivity induced by neutron bombardment, *Nature*, 1934, cxxxiii, 757.

<sup>3</sup> CHAIKOFF, I. L., and TAUROG, A.: Application of radioactive iodine to studies in iodine metabolism and thyroid function. In *The Use of Isotopes in Biology and Medicine*, 1948. University of Wisconsin Press, Madison.

in clinics located in close proximity to the cyclotron in which the element was produced. The eight-day isotope,  $I^{131}$ , now produced in adequate quantity by the atomic energy pile at Oak Ridge has extended the applicability of this element.

Physiological and clinical studies with radioiodine are fundamentally based upon the observations of Marine and his associates who, in 1915 and 1916,<sup>4, 5</sup> demonstrated the unique ability of the thyroid selectively to collect relatively large quantities of this element. The use of a labelled isotope has shed additional light upon certain basic problems associated with the metabolism of iodine. Such studies have usually been carried out with tracer doses of the isotope inadequate to produce a radiation effect upon the tissues, but nevertheless active enough to be detected by physical means. Localization as well as quantitation of radioiodine has been accomplished through the use of Geiger-Muller counters applied to the surface of the body over numerous areas. Additional information has been accumulated through the technic of autoradiography first employed by Hamilton, Soley and Eichorn.<sup>6</sup> By this ingenious method sections of thyroid containing radioiodine are found to produce a characteristic picture when placed against photographic film. Subsequent comparison of the developed film with identical histological sections permits localization of the isotope. Excretion of the element in urine and feces can be detected and quantitated by the Geiger counter.

It may be of interest to detail some of the pertinent information recently acquired by these methods. Werner, Quimby and Schmidt<sup>7</sup> observed, in a group of 30 normal individuals, that the average uptake of radioiodine by the thyroid was approximately 21 per cent of the ingested dose. In a group of 39 patients with thyrotoxicosis the average uptake was found to be approximately 58 per cent. Three individuals with non-toxic nodular goiters had an average uptake of 19 per cent, a figure closely approximating the normal. Five patients with hypothyroidism, on the other hand, had an average uptake of only 3 per cent. Other studies of similar character have yielded essentially similar results. It is apparent that the collection of iodine by the thyroid varies with the functional state of the gland. Such information has not only diagnostic value, but is of considerable therapeutic importance as will be emphasized below. It has been possible to duplicate these results by experimental means. Hertz et al.<sup>8, 9</sup> produced hyperplasia of the

<sup>4</sup> MARINE, D.: Quantitative studies on the in vivo absorption of iodine by dogs' thyroid glands, *Jr. Biol. Chem.*, 1915, xxii, 547.

<sup>5</sup> MARINE, D., and ROGOFF, J. M.: The absorption of potassium iodide by the thyroid gland in vivo following its intravenous injection in constant amounts, *Jr. Pharmacol. and Exper. Therap.*, 1916, viii, 439.

<sup>6</sup> HAMILTON, J. G., SOLEY, M. H., and EICHORN, K. B.: Deposition of radioactive iodine in human thyroid tissue, *Univ. California Publ. Pharmacol.* (No. 28), 1940, i, 339.

<sup>7</sup> WERNER, S. C., QUIMBY, E. H., and SCHMIDT, C.: The clinical use of radioactive iodine, *Bull. N. Y. Acad. Med.*, 1948, xxiv, 549.

<sup>8</sup> HERTZ, S., ROBERTS, A., MEANS, J. H., and EVANS, R. D.: Radioactive iodine as an indicator in thyroid physiology. II. Iodine collection by normal and hyperplastic thyroids in rabbits, *Am. Jr. Physiol.*, 1940, cxxviii, 565.

<sup>9</sup> HERTZ, S., and ROBERTS, A.: Radioactive iodine as an indicator in thyroid physiology. III. Iodine collection as a criterion of thyroid function in rabbits injected with thyrotropic hormone, *Endocrinology*, 1941, xxix, 82.

thyroid in animals by the feeding of a diet high in nitrile content (cabbage), and by the administration of the thyrotropic hormone of the pituitary. These hyperplastic glands were observed to have a greater affinity for iodine than the normal thyroid. Quantitation of the urinary excretion of the isotope offers adjunct evidence concerning iodine retention by the gland and is found to vary inversely with the percentage uptake by the thyroid.

Variations in the uptake of iodine by the thyroid can be produced by other experimental means some of which are of clinical interest. LeBlond et al.<sup>10</sup> noted that the exposure of rats to cold led to greater collection of iodine than normal and a doubling of the rate of excretion of iodized products. Anti-thyroid drugs, such as thiouracil and related compounds, first introduced in 1943,<sup>11</sup> are known to produce acinar hyperplasia paradoxically associated with a decrease in basal metabolic rate. The combined use of such compounds with radioiodine has resulted not only in verification but also extension of previous pharmacological hypotheses. Franklin, Lerner and Chaikoff<sup>12</sup> demonstrated that the feeding of thiouracil depresses the uptake of radioiodine by the rat thyroid and likewise retards its transformation into diiodotyrosine, and thyroxine. In this manner thiouracil blocks the formation of an iodinated hormone. Discontinuance of the drug was followed in a short time by a return to normal of the iodine concentrating capacity of the gland.

Clinicians have been puzzled for many years by the paradoxical yet beneficial effect of iodine upon patients whose thyroids were avid for the material and rapidly secreted the absorbed element as thyroid hormone. Rawson et al.<sup>13</sup> utilized radioiodine to study this phenomenon. In a typical patient with Graves' disease, administration of a tracer dose of radioiodine resulted in the urinary excretion of only 16.3 per cent indicative of a marked avidity for the drug. After treatment with thiouracil urinary excretion rose to 73.5 per cent. Treatment was continued with the combined use of thiouracil and radioiodine. Repeated urine studies indicated that virtually all of the labelled iodine was being excreted. At operation the gland was found to contain virtually no radioiodine. Yet, in spite of this, histological examination revealed involution of the hyperplastic gland. Rawson concluded that iodine exerts two actions on the thyroid, an iodinating action and an involuting one, in hyperthyroidism and that these two actions can be separated, one from the other, by means of thiouracil.

Many additional basic studies have been carried out with these agents which space limitations forbid mention of. Nevertheless, it is apparent

<sup>10</sup> LeBLOND, C. P., GROSS, J., PEACOCK, W., and EVANS, R. D.: Metabolism of radioiodine in the thyroids of rats exposed to high and low temperatures, *Am. Jr. Physiol.*, 1944, cxi, 671.

<sup>11</sup> ASTWOOD, E. B.: Treatment of hyperthyroidism with thiourea and thiouracil, *Jr. Am. Med. Assoc.*, 1943, cxxii, 78.

<sup>12</sup> FRANKLIN, A. L., LERNER, S. R., and CHAIKOFF, I. L.: The effect of thiouracil on the formation of thyroxine and diiodotyrosine by the thyroid of the rat with radioactive iodine as an indicator, *Endocrinology*, 1944, xxxiv, 265.

<sup>13</sup> RAWSON, R. W., MOORE, F. D., PEACOCK, W., MEANS, J. H., COPE, O., and RINDELL, C. B.: Effect of iodine on the thyroid gland in Graves' disease when given in conjunction with thiouracil: A two-action theory of iodine, *Jr. Clin. Invest.*, 1945, xxiv, 869.

that such information constituted an important foundation for clinical application of the various isotopes of iodine. Hamilton and Lawrence,<sup>14</sup> in 1942, reported that a single dose of 300 microcuries of  $I^{131}$ , injected subcutaneously, produced almost complete destruction of a dog's thyroid without pathological evidence of damage to any other vital tissues. This dose represented approximately 30 times the single dose which would be given to man. It is this destructive effect on thyroid tissue which is the basis for the therapeutic application of radioiodine. The selective internal irradiation achieved by radioiodine is obviously distinctly more precise and localized than external irradiation by roentgen-rays which had been in use, to a certain extent, for a number of years.

The first clinical application of radioiodine was in the treatment of thyrotoxicosis. In 1942 Hertz and Roberts<sup>15</sup> and Hamilton and Lawrence<sup>14</sup> reported observations on the treatment of small groups of such patients. Since then studies on several additional groups of patients have been reported in the literature. Nevertheless, even today the total number of individuals studied is relatively small. Before discussing some of the reported observations it may be well to review certain of the problems associated with the clinical use of radioiodine. Reference has already been made to the matter of selection of the suitable isotope. The greater availability of  $I^{131}$  and its longer half-life have made this isotope the one of choice in most recent studies. The mode of administration has usually been per os, in aqueous solution.

Calculation of proper dosage has constituted a great problem and as a result earlier studies in which certain variables were not determined must be analyzed in this light. The variables to be taken into account in determining effective dosage include, in addition to the number of millicuries of isotope administered, the percentage uptake by the gland, its size and the rate of elimination from the thyroid. The effective dose can be expressed in terms of equivalent roentgens. This is determined, theoretically, by assuming an even distribution of so many microcuries per gram of thyroid gland. Preliminary calculations which are in the realm of the radio-physicist must be made prior to administration of the isotope. The clinician contemplating the use of radioiodine should be assured of the collaboration of a physicist.

Since radioiodine uptake by the thyroid is influenced by previous iodine or antithyroid drug therapy, it is essential, for maximum collection, that such drugs be withdrawn for at least a two-week period prior to the administration of the isotope. Preliminary tracer studies should be done to determine percentage uptake in the particular patient. Estimation of gland size is accomplished by palpation, keeping in mind, for reference, that the average normal thyroid has a weight of 25 to 30 grams. Werner, Quimby and Schmidt<sup>7</sup> utilize plasticine models of various sizes for this admittedly crude

<sup>14</sup> HAMILTON, J. G., and LAWRENCE, J. H.: Recent clinical developments in the therapeutic application of radio-phosphorus and radio-iodine, Jr. Clin. Invest., 1942, xxi, 624.

<sup>15</sup> HERTZ, S., and ROBERTS, A.: Application of radioactive iodine in therapy of Graves' disease, Jr. Clin. Invest., 1942, xxi, 624.

method of estimation. These investigators have proposed a formula for determining radiation dosage based upon all the variables mentioned above. In terms of  $I^{131}$  they suggest a total radiation dose of approximately 6,000 equivalent roentgens or approximately 100 or more microcuries per gram of gland tissue.

It will be of interest to review briefly some of the clinical data obtained in the treatment of thyrotoxicosis. In 1946 Hertz and Roberts<sup>16</sup> reviewed experiences with a group of 29 cases which had been observed since 1941. These patients were treated with a mixture of  $I^{130}$  and  $I^{131}$  consisting predominantly of the former. The total radioactivity administered varied between 0.7 and 28 millicuries. In 19 cases this was given in a single dose and in the remaining 10 in divided doses. All patients received stable iodine in the form of saturated solution of potassium iodide for varying periods after the administration of the radioisotope. The rationale for the latter procedure was the assumption that continued administration of stable iodine would reduce the rate of release of the isotope from the gland. Subsequent experience indicated that this procedure was probably unnecessary. Therapeutic benefits observed in this series were definitely attributable to the radioisotope. Twenty patients, followed for periods up to four years, were considered cured by all clinical and laboratory standards. In the remaining nine the treatment was considered ineffective. Five of these patients, who were subsequently sub-totally thyroidectomized, developed post-operative hypometabolism. No unusual complications were noted in the entire group. The incidence of successful therapy in this group, therefore, was 69 per cent.

Chapman and Evans<sup>17</sup> treated 22 patients with thyrotoxicosis during the period 1943 to 1945. These patients received 0.5 to 1 millicurie of  $I^{130}$  per estimated gram of thyroid tissue. The average total dose per patient was 40 to 50 millicuries. Fourteen patients responded well to a single dose; three required two doses and five had to be given three doses. No other therapy was used. Four patients subsequently developed myxedema and two, although improved, still were mildly hyperthyroid. Werner, Quimby and Schmidt<sup>7</sup> have treated 40 patients with toxic goiter with  $I^{131}$ . Eighteen had received no previous treatment, while 22 were recurrent after operation and had received antithyroid drug therapy for some time without satisfactory relief. All patients in this group received 3 to 4 millicuries of  $I^{131}$  which was calculated to give an effective dose of 3–5,000 equivalent roentgens. Maintenance of a standard dose resulted in patients with large thyroids receiving less radiation than others with smaller glands. This dosage schedule was deliberately adhered to for study purposes. Twenty-seven patients required only a single dose for complete control. Three additional patients responded well after a second dose. Six patients had been treated just prior to the

<sup>16</sup> HERTZ, S., and ROBERTS, A.: Radioactive iodine as an indicator in the study of thyroid physiology. VII. The use of radioactive iodine therapy in hyperthyroidism, *Jr. Am. Med. Assoc.*, 1946, cxxxix, 81.

<sup>17</sup> CHAPMAN, E. M., and EVANS, R. D.: The treatment of hyperthyroidism with radioactive iodine, *Jr. Am. Med. Assoc.*, 1946, cxxxix, 86.

report and could not be evaluated. Four frank failures occurred. A successful result occurred therefore, in 30 of 34 patients, an incidence of 88 per cent. Analysis of the failures seems to implicate inadequate dosage attributable chiefly to disproportion between the size of the gland and the dose of isotope. Soley and Miller<sup>18</sup> have reported observations on 33 patients treated with I<sup>131</sup> and followed for a period of three months to two years. Seventy-five per cent of the patients experienced a satisfactory remission.

In general, successfully treated patients experience a return to a normal basal metabolic rate by the end of the second or the middle of the third month after administration of the isotopes. In most instances the gland likewise returns to normal size in a similar period of time. Histological examination of such glands reveals loss of acinar tissue and resultant fibrosis. Soley and Miller performed serial ophthalmometric measurements on 26 of their patients. Seventeen exhibited no changes; one patient had a decrease in exophthalmos of 1.5 mm.; six patients had an increase in exophthalmos of 1.5 to 2.5 mm. Two patients developed severe exophthalmos and were later treated with thyroid extract. These authors believe that the changes in ocular findings compare favorably with those seen in other modes of therapy.

A consideration of the complications of radioiodine therapy must include not only the patient but also the physician and others associated with the treatment. The hazards to the patient may be of a more or less immediate nature or of long-term significance. There were no fatalities in any of the groups studied. Nor did tetany or loss of phonation occur. In a few instances symptoms resembling radiation sickness, of a transient character, occurred. Several instances of laryngeal irritation with cough and sore throat were observed and occasionally tenderness of the gland was present for a short time. In three patients of Werner, Quimby and Schmidt's group a transient increase in toxicity was seen. This was considered to be due to tissue necrosis with rapid release of large quantities of thyroid hormone. In several of the groups studied transient or sustained hypothyroidism developed. The relation of dosage to this phenomenon was usually evident. There were no disturbances of hematopoietic function in any of the reported cases. In view of the urinary excretion of the isotope studies of renal function were carried out in some instances, but no dysfunction was noted. Consideration of long term hazards with radioactive isotope therapy must include mention of the possibility of late malignancy. It is the consensus of opinion based, not only on isotope therapy, but also on previous experience with the roentgen treatment of thyrotoxicosis, that later malignant changes are unlikely.

Workers with radioactive isotopes must be fully cognizant of the hazards of excessive radiation. Rules for health protection issued by the Atomic

<sup>18</sup> SOLEY, M. H., and MILLER, E. R.: Treatment of Graves' disease with radioactive iodine, *Med. Clin. N. Am.*, 1948, 3-17.

Energy Commission should be followed in any laboratory or clinic using these materials. During the first 24 to 72 hours after administration of radioactive iodine the patient's urine will be radioactive and measures for proper isolation and disposal must be taken.

The physician charged with the responsibility of the proper management of the patient with thyrotoxicosis has, today, a choice of three relatively satisfactory methods of therapy. Surgical management has steadily improved and in some clinics operative mortality has been reduced to under 1 per cent. Nevertheless, the ordeals attendant upon an operation remain. The introduction of propylthiouracil, with consequent diminution of toxic reactions, has improved the outlook for the medical management of the disease. Such therapy must often be maintained, however, over a period of a year or more with some uncertainty still existing concerning the permanence of remission following discontinuance of the drug. With radioiodine therapy problems of dosage still remain to be clarified. In addition, although the probability of late malignancy seems slight, a further period of time must elapse before this doubt can be resolved with certainty. Most workers in the field agree that, at present, isotope therapy should be used only in those centers equipped for adequate follow-up studies as well as facilities for careful measurement of dosage, and protection of personnel against radiation hazards. It is of course obvious that each of these methods of therapy is aimed at an etiology which is still imperfectly understood. The clarification of etiological mechanisms may in the future point the way toward an even more rational therapeutic attack upon the disease.

One can hardly leave the subject of radioactive iodine therapy without brief mention of its use in malignancy of the thyroid. Internal irradiation of neoplastic thyroid tissue in the neck as well as in distant metastatic foci would, at first glance, appear to offer considerable therapeutic possibilities. However, in 1940, Hamilton et al.<sup>6</sup> noted on clinical trial that the isotope was not deposited within carcinomatous areas of the gland. Subsequently, however, Keston et al.<sup>19</sup> were able to demonstrate an appreciable uptake of the isotope not only in well-differentiated metastases of an adenocarcinoma of the thyroid but also a small uptake by less well differentiated metastases in the same case. Seidlin, Marinelli and Osbry<sup>20</sup> have reported treatment of a patient with adenocarcinoma of the thyroid which was simultaneously accompanied by signs of hyperthyroidism. The thyrotoxicity was apparently due to hyperfunctioning metastases since the gland itself had been completely removed. Over a period of time this patient received 75 millicuries of I<sup>130</sup> and 65 millicuries of I<sup>131</sup>. Observation of the patient for three years revealed no clinical evidence of renal or other visceral involvement. The hyperthyroidism responded fully, but the metastases, although controlled, did not

<sup>19</sup> KESTON, A. S., BALL, R. P., FRANTZ, V. K., and PALMER, W. W.: Storage of radioactive iodine in a metastasis from thyroid carcinoma, *Science*, 1942, xcv, 362.

<sup>20</sup> SEIDLIN, S. M., MARINELLI, L. D., and OSBRY, E.: Therapeutic effect of radioactive iodine on functioning metastases of thyroid adenocarcinoma, *Jr. Am. Med. Assoc.*, 1946, cxxxii, 838.



disappear. This case is of further interest in that it demonstrated that massive dosages of radioactive iodine, far in excess of currently used dosages in hyperthyroidism, failed to produce any deleterious effects upon the kidney or hematopoietic tissue during a three year period of observation.

The largest group of cases of malignant disease of the thyroid treated with radioiodine reported to date is that of Marinelli et al.<sup>21</sup> These investigators studied the uptake of radioiodine in 19 cases of thyroid carcinoma. The extent of iodine collection appears to be related to the histopathology of the tumor. In general, well differentiated tumors absorb more of the isotope than anaplastic neoplasms. On the basis of the incidence of various histological types of thyroid malignancies only about 15 per cent of thyroid cancers may be expected to accumulate radioactive iodine to some degree. In view of the well known pleomorphism of thyroid cancer a decision concerning the therapeutic value of radioiodine cannot be based on a single small biopsy, but should be made only after preliminary tracer study. Future investigations into the therapeutic application of radioiodine in thyroid malignancy will be concerned with methods for increasing the iodine collecting properties of the tumor. At present surgical removal of as large a portion of malignant and normal thyroid tissue as possible is indicated, since this not only diminishes the amount of tissue to be irradiated, but may also increase the efficiency of subsequent uptake of the isotope. The preliminary use of thyrotropic hormone as well as means for temporarily blocking the renal excretion of the isotope is at present under investigation.

M. S. S.

<sup>21</sup> MARINELLI, L. D., FOOTE, F. W., HILL, R. F., and HOCKER, A. F.: Retention of radioactive iodine in thyroid carcinomas: Histopathologic and radio-autographic studies, *Am. Jr. Roentgenol.*, 1947, lviii, 17.

## REVIEWS

*Principles of Hematology.* 3rd Ed. By RUSSELL L. HADEN. 366 pages; 15.5 × 24 cm. Lea & Febiger, Philadelphia. 1946. Price, \$5.00.

The third edition of this volume presents a brief and somewhat elementary survey of the field of Hematology. The merit of a simple introduction to a complex field such as this cannot be denied but the presentation would be distinctly more valuable with the addition of a carefully selected bibliography designed to assist the interested reader. The bibliography is quite scanty and most references are to reports published prior to 1939. Many recent developments in hematology such as the use of folic acid in the macrocytic anemias and nitrogen mustard in the leukemias and lymphomata are not discussed at all. The book is abundantly illustrated but most of the illustrations, although technically good, are in black and white and are insufficiently magnified to be of any great help to the novice for whom the book is intended.

M. S. S.

*The Management of Obesity.* By LOUIS PELNER, M.D., Associate Physician. Green-Point Hospital, Brooklyn, New York. 144 pages; 15 × 22.5 cm. Personal Diet Service, New York, N. Y. 1946.

This is a small, handy, readable book that tells in a few pages many of the elementary facts about the problems of overweight due to excess fat. Actuarial philosophy is liberally added in the early pages. The short chapters bounce somewhat unevenly from practicalities of treatment to etiological association with some rare diseases. Unnecessary emphasis is given to 'endogenous' obesity and to elaborate recommendations regarding exercise. There are some effective diagrams and a useful summary of nutritional factors and values.

C. B. A.

*Viral and Rickettsial Infections of Man.* Edited by THOMAS M. RIVERS, M.D., Director of the Hospital, The Rockefeller Institute for Medical Research. 587 pages; 26.5 × 18 cm. J. B. Lippincott Company, Philadelphia. 1948. Price, \$5.00.

The editor has assembled an imposing list of authorities to write the different sections of this volume. Nearly all of the better known names of American workers in the viral and rickettsial diseases are listed among the contributors. The book is an authoritative statement of the status of our knowledge in this field. So rapid have been the advances in recent years that such a symposium will greatly lighten the task of the physician who otherwise would have to search the profuse and widely scattered journal literature.

The first seven chapters are devoted to the methods employed in the study of viral and rickettsial agents. After an introductory chapter by Thomas M. Rivers on the general nature of these agents and the infections due to them there are chapters on physical and chemical procedures (W. M. Stanley and Max A. Lauffer); serological reactions (Joseph E. Smadel); chick-embryo technics (E. W. Goodpasture and G. John Buddingh); propagation in tissue culture (John F. Enders); epidemiology (Kenneth F. Maxcy); and bacteriophages (A. D. Hershey and J. Bronfenbrenner). These chapters constitute a most valuable summary and critique of the investigative methods in this difficult field. Every student of the viral and rickettsial disease problems will benefit by this well organized presentation.

The remainder of the book, approximately 400 pages, is devoted to the different diseases and disease groups of known viral and rickettsial origin. These chapters are not written by clinicians for clinicians but by scientific investigators who are interested primarily in disease. A uniform outline has been employed: Introduction;

history; clinical picture; pathological picture; experimental infection, host range; etiology; diagnosis; treatment. The emphasis is on the characteristics of the etiological agent, the immunologic processes concerned, the diagnostic procedures in man and animals and on epidemiology. It is of course these aspects of these diseases in which research has been and is so active and so fruitful.

The selection of authors has naturally been on the basis of their contributions to knowledge of these aspects of the diseases described. Other investigators, pathologists, bacteriologists, internists will find the chapters on the separate diseases an invaluable reference.

The sections on the "clinical picture" are of varying value. On the whole they make little attempt to more than outline the common clinical characteristics. References to the clinical literature are relatively few. Questions of treatment are often sketchily dealt with, and in some instances appear too dogmatic. The principles of disease control are discussed but not the practical details of application. In brief, the practicing physician and the field worker in disease prevention will gain deeper understanding of basic processes in the diseases discussed but not all that he might want in clinical detail, for use at the bedside, or of practical methods for a control program.

Within its scope there is no single text which is so adequate. It fills a very real need and should meet a warm welcome.

M. C. P.

### BOOKS RECEIVED

Books received for September are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*A-B-C's of Sulfonamide and Antibiotic Therapy.* By PERRIN H. LONG, M.D., F.R.C.P., Professor of Preventive Medicine, The Johns Hopkins University School of Medicine, etc. 231 pages; 19 × 11.5 cm. 1948. W. B. Saunders Company, Philadelphia. Price, \$3.50.

*Bronchiogenic Carcinoma and Adenoma, with a Chapter on Mediastinal Tumors.* By B. M. FRIED, M.D., Associate Attending Physician, Montefiore Hospital for Chronic Diseases, New York. 306 pages; 23.5 × 16 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$6.00.

*Changing Disciplines: Lectures on the History, Method and Motives of Social Pathology.* By JOHN A. RYLE, M.D., Professor of Social Medicine in the University of Oxford, etc. 123 pages; 19 × 12.5 cm. 1948. Oxford University Press, New York. Price, \$3.75.

*Clinical Roentgenology of the Digestive Tract.* 3d Ed. By MAURICE FELDMAN, M.D., Assistant Professor of Gastroenterology, University of Maryland, etc. 901 pages; 24 × 16 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$8.00.

*Detailed Atlas of the Head and Neck.* By RAYMOND C. TRUEX, M.S., Ph.D., Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia University; and CARL E. KELLNER, Artist, Department of Anatomy, College of Physicians and Surgeons, Columbia University. 162 pages; 31.5 × 24.5 cm. 1948. Oxford University Press, New York. Price, \$15.00.

*Handbook of Orthopaedic Surgery.* 3d Ed. By ALFRED RIVES SHANDS, JR., B.A., M.D., Medical Director of the Alfred I. duPont Institute of the Nemours Foundation, Wilmington, etc.; in collaboration with RICHARD BEVERLY RANEY, B.A., M.D., Associate in Orthopaedic Surgery, Duke University School of Medicine, Durham, etc.; Illustrated by JACK BONACKER WILSON. 574 pages; 22.5 × 14.5 cm. 1948. The C. V. Mosby Company, Saint Louis. Price, \$6.00.

- Hospital Trends and Developments, 1940-1946.* Edited by ARTHUR C. BACHMEYER, M.D., Director, University of Chicago Clinics, etc., and GERHARD HARTMAN, Ph.D., Superintendent, University Hospitals, etc. 819 pages; 24.5 × 16 cm. 1948. The Commonwealth Fund, New York. Price, \$5.50.
- Lecciones de Patología Médica (Enfermedades del Hígado).* Tomo VI. By DR. C. JIMENEZ DIAZ. 998 pages; 25 × 17.5 cm. 1948. Editorial Científico-Médica, Madrid.
- Management in Obstetrics.* By ANDREW M. CLAYE, M.D., F.R.C.S., F.R.C.O.G., Professor of Obstetrics and Gynaecology, University of Leeds, etc. 186 pages; 19 × 12.5 cm. 1948. Oxford University Press, New York. Price, \$3.75.
- Medical Research in France During the War (1939-1945).* Thirty articles gathered and presented by JEAN HAMBURGER, Professor agrégé à la Faculté de Médecine, Médecin des Hôpitaux de Paris. Foreword by PROFESSEUR PASTEUR VALLERY-RADOT, Membre de l'Institut. 306 pages; 25.5 × 16.5 cm. (paper-bound). 1948. Éditions Médicales Flammarion.
- Microbiology and Pathology.* 4th Ed. By CHARLES F. CARTER, B.S., M.D., Instructor in Pathology and Applied Microbiology, Parkland Hospital School of Nursing, Dallas, etc. 845 pages; 22.5 × 14.5 cm. 1948. The C. V. Mosby Company, Saint Louis. Price, \$5.00.
- Occupational Marks and Other Physical Signs: A Guide to Personal Identification.* By FRANCESCO RONCHESE, M.D., Instructor in Dermatology, Boston University School of Medicine, etc.; Foreword by JOHN G. DOWNING, M.D., Professor of Dermatology, Boston University School of Medicine, etc. 181 pages; 23.5 × 16 cm. 1948. Grune & Stratton, Inc., New York. Price, \$5.50.
- Pharmacology.* 3d Ed. By J. H. GADDUM, ScD., F.R.S., M.R.C.S., L.R.C.P., Professor of Pharmacology in the University of Edinburgh. 504 pages; 22.5 × 14 cm. 1948. Oxford University Press, New York. Price, \$8.00.
- Polio and Its Problems.* By ROLAND H. BERG, with a Foreword by BASIL O'CONNOR, President, The National Foundation for Infantile Paralysis, Inc. 174 pages; 23.5 × 16 cm. 1948. J. B. Lippincott Company, Philadelphia. Price, \$3.00.
- A Practical Manual of the Diseases of the Chest.* 3d Ed. By MAURICE DAVIDSON, M.A., M.D. Oxon., F.R.C.P. Lond., Physician to the Brompton Hospital for Consumption and Diseases of the Chest, etc. 670 pages; 25 × 17.5 cm. 1948. Oxford University Press, New York. Price, \$16.50.
- Reticulosis and Reticulosarcomatosis: A Clinical and Pathological Study.* By DR. P. VAN DER MEER and DR. J. ZELDENRUST, from the Medical Clinic of the University Hospital, Leyden, Holland, etc. 99 pages; 24.5 × 16 cm. 1948. Universitaire pers Leiden, Leyden, The Netherlands. Price: guilders 4.90.
- Sterility and Impaired Fertility: Pathogenesis, Investigation and Treatment.* 2nd Ed. By CEDRIC LANE-ROBERTS, C.V.O., M.S., F.R.C.S., F.R.C.O.G., Gynaecological Surgeon, Royal Northern Hospital, etc.; ALBERT SHARMAN, M.D., Ph.D., M.R.C.O.G., Senior Assistant Surgeon, Royal Samaritan Hospital for Women, Glasgow, etc.; KENNETH WALKER, M.A., M.B., B.C. (Cantab), F.R.C.S., F.I.C.S., Jacksonian Prizeman and Hunterian Professor, Royal College of Surgeons, etc.; B. P. WIESNER, D.Sc., Ph.D., F.R.S.E., Consulting Biologist, Royal Northern Hospital, and MARY BARTON, M.B., B.S., First Assistant to the Fertility Clinic, Royal Free Hospital, London. 400 pages; 22.5 × 14.5 cm. 1948. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, \$6.50.
- Symposia on Nutrition of The Robert Gould Research Foundation. Volume I: Nutritional Anemia.* Edited by ARTHUR LEJWA. 194 pages; 23.5 × 15 cm. 1948. The Robert Gould Research Foundation, Inc., Cincinnati. Distributed without cost to individuals and organizations interested in nutritional problems.

# COLLEGE NEWS NOTES

## PROPOSAL OF CANDIDATES

The By-Laws of the American College of Physicians require that proposals of candidates for election to Associateship or Fellowship be filed at least 60 days in advance of action by the Credentials Committee. The next meetings of the Committee are scheduled for February 26 and 27, 1949, and March 26, 1949.

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## ASSOCIATES SHOULD ATTEND A.C.P. ANNUAL SESSION

Attendance at one or more Annual Sessions by Associates before proposal for advancement to Fellowship is prescribed by regulations of the Board of Regents of the American College of Physicians. This regulation was temporarily discontinued during World War II, from 1942 to 1946, because it became obviously impossible for Associates in the armed services to attend and because the Annual Sessions of the College had to be abandoned during part of that time. The regulation is now again in full effect. It is maintained that an Associate must display an abiding interest in the College and in internal medicine or its allied branches. There is no better way in which such an interest can be displayed than by attendance at the Annual Sessions of the College, accepted as the most important postgraduate week in the field on this Continent.

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## 1948 MEMBERSHIP ROSTER DISTRIBUTED

The Board of Regents and Officers of the American College of Physicians had hoped to be able to resume publication this year of a complete College Directory. This was found to be impossible, however, because of continued shortage of printing labor and excessively high production costs, and so authorization was given to print the 1948 MEMBERSHIP ROSTER, in which biographical data of members are omitted.

The Membership Roster contains lists of the Boards of Regents and Governors, Officers, and Committees; the full Constitution and By-Laws, as amended May 1, 1947, and April 22, 1948; a statement of the College's Awards and Fellowships; and the alphabetic and geographic (with specialty designations) rosters of members as of August 1, 1948.

The Roster has now been mailed to all members of the College in good standing. If any have failed to receive their copies, they are requested so to inform the Executive Secretary of the College. Also, it is desired that the Executive Secretary be notified of any corrections or omissions in the Roster listings.

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## A.C.P. POSTGRADUATE COURSES

### *Autumn, 1948 Schedule*

It is gratifying to report that the postgraduate courses of the American College of Physicians on the Autumn, 1948 schedule have all been well supported and that there was even a further improvement in the quality, scope and teaching over the same preceding courses. There remain on the program two courses, No. 7, CARDIOVASCULAR DISEASE, Emory University School of Medicine, Atlanta, Bruce Logue, M.D., F.A.C.P., Director, one week—December 6-11; and No. 8, GASTRO-ENTEROLOGY, Graduate Hospital of the University of Pennsylvania, Philadelphia, H. L. Bockus, M.D., F.A.C.P., Director, one week—December 6-11. At the time of preparation of this news item (October 13, 1948) both courses are still open for additional registrations.

*Spring, 1949 Schedule*

Following is the tentative schedule of courses under consideration by the Advisory Committee on Postgraduate Courses for the Spring of 1949.

(1) GASTRO-ENTEROLOGY—University of California Medical School and Stanford University School of Medicine, San Francisco, Calif.; T. L. Althausen, M.D., F.A.C.P., and Dwight L. Wilbur, M.D., F.A.C.P., Directors; one week, February 7-12.

This course is open for registration, although the outline is not published. These very capable Directors are organizing an outstanding course which should be exceedingly popular with members of the College, especially those from the West and Far West. Dr. Cecil Watson, Professor of Medicine at the University of Minnesota Medical School, will be one of the guest clinicians.

(2) HEMATOLOGY—Ohio State University College of Medicine, Columbus, Ohio; Charles A. Doan, M.D., F.A.C.P., Director; one week, February 14-19.

This is a repetition of previous, excellent courses that Dr. Doan has organized for the College. It is a course of exceptional merit in its field.

(3) PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE—University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Julius H. Comroe, Jr., M.D., F.A.C.P., Director; one week, May 9-14.

This is a repetition of the most unusual and popular course organized by Dr. Comroe one year ago when the registration rose to 189. It is planned for internists who are interested in learning why symptoms occur, how drugs act, and why and how clinical physiological tests are used in diagnosis. It is designed—not along lines of the theoretical physiology taught in many undergraduate medical schools—but rather along newer concepts of teaching dynamic clinical physiology to practicing physicians. The faculty will consist of many authorities from Philadelphia institutions, and also outstanding teachers and authorities from Boston, New York, Baltimore, Chicago, Cleveland, and elsewhere.

(4) INTERNAL MEDICINE—Massachusetts General Hospital, Boston, Mass.; James H. Means, M.D., F.A.C.P., Director; two weeks—dates yet to be determined.

Dr. Means is Jackson Professor of Clinical Medicine, Harvard Medical School, and Chief of Medical Services, Massachusetts General Hospital. He and his faculty are known everywhere for the excellence of their exceedingly fine work. They have not given a course for the College for a few years, and this will be an exceptional opportunity for members to take this fine course in Boston.

(5) CARDIOLOGY—Philadelphia Institutions; William G. Leaman, Jr., M.D., F.A.C.P., Director; one week—dates yet to be determined.

This course is under discussion with Dr. Leaman and other participating teachers in the Philadelphia area. The faculty will consist of leading teachers in Cardiology from various medical schools of Philadelphia and other institutions of the East. The course has been given on previous occasions with signal success.

(6) DISEASES OF THE CHEST—Creighton University School of Medicine and the University of Nebraska College of Medicine, Omaha, Nebr.; J. D. McCarthy, M.D., F.A.C.P., Director; one week—dates yet to be determined.

This course is still in the formative state, under discussion by the Director and members of the faculties of the two named institutions. It is possible that the title of the course may be changed. Watch these columns for further announcements.

(7) **ELECTROCARDIOGRAPHY**—Massachusetts General Hospital, Boston, Mass.; Conger Williams, M.D., Director; one week—dates yet to be determined.

This will be a repetition of the course given for the College by Dr. Williams during May, 1948. It is designed to acquaint the student with modern theory of electrocardiography and its clinical application. The opening days will be devoted to lectures on the theory of electrocardiography and an attempt will be made to present the current points of view. Since it is impossible to teach electrocardiographic interpretation in so short a time, the course should be limited to those who have had some previous experience in the field. By presenting many electrocardiograms from the laboratory, there will be sufficient material to cover the most important representative patterns. The chief aim of this course will be to teach interpretation based on current knowledge of the physiology of heart muscle. All the exercises in practical interpretation will include the new leads.

(8) **ENDOCRINOLOGY**—Tufts College Medical School, Boston, Mass.; Edwin B. Astwood, M.D., Director; one week—dates yet to be determined.

This course is still tentative on the schedule, but arrangements are being consummated through Dr. Robert P. McCombs, F.A.C.P., Director of Postgraduate Teaching at Tufts College Medical School. Dr. Astwood is Research Professor of Medicine at Tufts College Medical School, and Endocrinologist to the Pratt Diagnostic Hospital. He is a recognized authority in the field of Endocrinology and a teacher of note.

(10) **MEDICAL ASPECTS OF RADIOACTIVITY**—Bureau of Medicine and Surgery, U. S. Navy, Medical Department of the U. S. Army, the Armed Forces Special Weapons Project, the Atomic Energy Commission, the Air Force and the U. S. Public Health Service, Washington, D. C.; Lt. Col. Karl Houghton, (MC), USA, Chairman.

It is not yet determined whether the course will be one, two, or three weeks in duration, nor have the dates been selected. The Surgeons General of the three services will cooperate wholeheartedly with the Armed Forces Special Weapons Project, and every effort is being made to procure the best talent available. Only a nominal registration fee will be charged. No fee whatsoever will be charged to medical officers, regular and reserve, of the Army, Navy, and Public Health Service. Details of the course are not yet fully available. An effort will be made to include the nature of ionizing radiation as it relates to atomic fission, the methods of detection and evaluation of the hazard, the biological effects of radiation, the possibilities of protection and avoidance, and present concepts of treatment. It is an obligation of the medical profession to inform themselves in this very important subject.

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#### A.C.P. REGIONAL MEETINGS

The *North Carolina* regional meeting of the College will take place at Chapel Hill on Friday, December 3, under the Governorship of Dr. Paul Whitaker, F.A.C.P. Edward McG. Hedgpeth, M.D., F.A.C.P., is chairman of the Program Committee.

The *Eastern Pennsylvania* regional meeting will take place in Philadelphia on December 10. Dr. Edward L. Bortz, F.A.C.P., the local Governor, has arranged an interesting program at the College of Physicians and Surgeons of Philadelphia, including a number of papers being presented that day in the A.C.P. postgraduate course in Gastroenterology (Henry L. Bockus, M.D., F.A.C.P., Director). A reception and dinner will be held in the evening at the Hotel Warwick.

The annual *Oklahoma* regional meeting was held at Tulsa on September 25, under the Governorship of Dr. Wann Langston, F.A.C.P., of Oklahoma City. Dr. LeRoy H. Sloan, F.A.C.P., Chicago, a Regent of the College, was the chief guest speaker and official representative of the Board. There were in attendance 38 Fellows from Oklahoma, 9 Fellows from other states, 11 Oklahoma Associates and one Associate from another state. In addition there were 59 guests, several of whom have proposals for membership now outstanding. Present also were the Deans of the Medical Schools of the University of Oklahoma and the University of Arkansas. A great deal of interest was displayed in the scientific program, in which papers were presented by Dr. William K. Ishmael, F.A.C.P., W. Floyd Keller, M.D., F.A.C.P., John H. Lamb, Jr., M.D., F.A.C.P., and Wann Langston, M.D., F.A.C.P.; Moorman P. Prosser (Associate); Arthur A. Hellbaum, M.D., Ph.D., and Cleve Beller, M.D., guests; Oklahoma City; D. W. Gillick, M.D., F.A.C.P., Talihina; E. Rankin Denny, M.D., F.A.C.P., and Samuel Goodman, F.A.C.P.; Paul Strong, M.D., and Averill Stowell, M.D., guests; Tulsa; Euclid M. Smith, M.D., F.A.C.P., Hot Springs, Ark.; LeRoy H. Sloan, M.D., F.A.C.P., Chicago; and Harold H. Jones, Sr., F.A.C.P., Winfield, Kans.

The *Iowa* regional meeting, at the Des Moines Club on October 9, was held under the Governorship of B. F. Wolverton, M.D., F.A.C.P., Cedar Rapids, who was ably assisted in the program arrangements by Drs. George E. Mountain, F.A.C.P., John C. Parsons, F.A.C.P., and Maurice J. Rotkow, F.A.C.P. Following a business meeting and luncheon, papers were presented by the following: Forest H. Coulson, M.D. (Associate), Burlington, Coronary Occlusion or Pulmonary Embolism?; Paul W. Berney, M.D. (Associate), Cedar Rapids, Senile Osteoporosis; Lawrence J. Halpin, M.D. (Associate), Cedar Rapids, Dosage Tolerance in Respiratory Allergy; Charles F. Lowry, M.D. (Associate), Council Bluffs, Fibrositis: Diagnosis and Treatment; Leon J. Galinsky, M.D., F.A.C.P., Des Moines, Bronchiogenic Carcinoma: A Clinical Dilemma; Arthur G. Lueck, M.D. (Associate), Des Moines, Etiology of Diabetes Mellitus: Current Concepts; P. G. Keil, guest, Des Moines, Angiocardiology; William B. Bean, M.D. (Associate), Iowa City, Cerebral Manifestations of Acute Myocardial Infarction; Henry Hamilton, M.D., guest, Iowa City, Cooley's Anemia; Leslie W. Swanson, M.D. (Associate), Mason City, X-Ray for Bronchial Asthma. A reception and dinner completed the program.

The first A.C.P. regional meeting in *Arkansas* was scheduled for October 30 at Hot Springs. Arless A. Blair, M.D., F.A.C.P., Fort Smith, Governor for Arkansas, presided at the banquet at which the speakers were Joseph T. Roberts, M.D., F.A.C.P., Dean of the University of Arkansas School of Medicine, and Dr. William D. Stroud, F.A.C.P., Philadelphia, A.C.P. Treasurer. Dr. Euclid M. Smith, F.A.C.P., was local Chairman of Arrangements. Dr. George B. Fletcher, F.A.C.P., presided over the afternoon meeting. The following papers were listed: A Report of 15 Cases of Tularemia with Special Reference to Results of Treatment, Captain Richard R. Taylor, (M.C.), U.S.A., guest, Hot Springs; Hemochromatosis—Case Report of a White Female without Diabetes Mellitus, Charles T. Chamberlain, M.D., F.A.C.P., Fort Smith; Adrenal Cortical Syndrome in Children, William A. Reilly, M.D., guest, Little Rock; Antibiotic Treatment of Pertussis, P. J. Almaden, M.D., Ph.D., guest, Little Rock; Current Problems in Research upon Nutritional Anemias, Paul L. Day, Ph.D., guest, Little Rock; The Myocarditis Problem, Robert H. Bayley, M.D., F.A.C.P., Oklahoma City, Okla.



The *Southeastern* Regional Meeting of the College, arranged through the co-operation of E. Dice Lineberry, M.D., F.A.C.P., Birmingham, Governor for Alabama, William C. Blake, M.D., F.A.C.P., Tampa, Governor for Florida, Carter Smith, M.D., F.A.C.P., Atlanta, Governor for Georgia, Robert Wilson, Jr., M.D., F.A.C.P., Charleston, Governor for South Carolina, and Jose J. Centurion, M.D., F.A.C.P., Havana, Governor for Cuba, will be held at the Academy of Medicine in Atlanta on December 4. William R. Minnich, M.D., F.A.C.P., Atlanta, is Chairman of the Committee on Arrangements. Dr. Walter W. Palmer, A.C.P. President, New York City, Dr. James E. Paullin, M.A.C.P., Atlanta, and Mr. Edward R. Loveland, A.C.P. Executive Secretary, are listed as speakers at the banquet in the Biltmore Hotel. The scientific session will include the following speakers: Paul E. Beeson, M.D., guest, Atlanta, Current Trends in Antibiotic Therapy; Walter Bauer, M.D., F.A.C.P., Boston, Diagnosis and Treatment of Gout; Walter H. Cargill, M.D., guest, Atlanta, Present-day Concepts of the Medical Treatment of Hypertension; David James, M.D., guest, Atlanta, The Management of Dicumarol Administration; Heinz Weems, M.D., and James Warren, M.D., guests, Atlanta, The Intracardiac Dynamics, as Illustrated by Diodrast Media (Moving Picture); Osler Abbott, M.D., guest, Atlanta, Management of Pulmonary Emphysema; Arthur Merrill, M.D., guest, Atlanta, Rôle of Potassium in Certain Medical and Surgical Conditions; William A. Smith, guest, Atlanta, Newer Drugs in the Treatment of Epilepsy.

Continuing the multi-state regional meetings so successfully started during the war, Governors and members of the College in Illinois, Indiana, Michigan, Minnesota and Wisconsin collaborated to produce the 1948 *Midwest* Regional Meeting at the Book-Cadillac Hotel, Detroit, on November 20. The host Governor was Dr. Douglas Donald, F.A.C.P., of Detroit, assisted by the Program Committee of which Dr. H. M. Pollard, F.A.C.P., Ann Arbor, was Chairman, and the Committee on Arrangements, Dr. Edward D. Spalding, F.A.C.P., Detroit, Chairman. The following presented papers: Gordon B. Myers, M.D., F.A.C.P., H. A. Klein, M.D., and T. Hiratzka, M.D., guests, Detroit, Correlation of Electrocardiographic and Pathologic Findings in Anterolateral Infarction; Franklin Johnston, M.D., guest, Ann Arbor, Common Errors in Interpretation of the Electrocardiogram; B. F. Ziegler, M.D., guest, Detroit, Diagnostic Problems in Congenital Heart Disease; Mitchell A. Spellberg, M.D., F.A.C.P., Chicago, Clinical Aspects of Unusual Cases of Small Bowel Disease; M. H. Streicher, M.D., guest, Chicago, Recent Trends in the Management of Chronic Ulcerative Colitis; Samuel F. Haines, M.D., F.A.C.P., and F. R. Keating, M.D., guest, Rochester, Minn., Use of Radio-iodine in the Treatment of Exophthalmic Goiter; Frank H. Bethell, M.D., F.A.C.P., Ann Arbor, Newer Methods in the Treatment of Leukemia; Frank Hartman, M.D., guest, Detroit, Problems in Internal Medicine—Studies with the Oxyhemograph (Continuous Recordings of Blood Oxygen); R. Frisch, M.D., guest, and Maurice A. F. Hardgrove, M.D., F.A.C.P., Madison, Wis., Evaluation of Newer Methods in the Diagnosis and Treatment of Peripheral Arterial Disorders; Richard B. Capps, M.D., F.A.C.P., Chicago, Clinical Aspects of Sequelae of Acute Hepatitis; Robert M. Kark, M.D., guest, Chicago, Present Status of Albumin Therapy in Chronic Hepatitis; D. Myers, M.D., guest, Detroit, Boeck's Sarcoid; Bradley M. Patten, M.D., guest, Ann Arbor, Micro-moving Pictures Showing Age Changes in the Character of the Embryonic Heart Beat; Thomas Francis, Jr., M.D., guest, Ann Arbor, Immunity to Poliomyelitis; Elwood A. Sharp, M.D., F.A.C.P., and E. H. Payne, M.D., guest, Detroit, The Effectiveness of Chloromycetin in the Treatment of Rickettsial Disease; Jerome W. Conn, M.D., F.A.C.P., Ann Arbor, Sweat Electrolytes in the Diagnosis of Abnormal Adrenal Cortical Function; W. P. Daines, M.D., guest, and Walter H. Nadler, M.D., F.A.C.P., Chicago, Routine Use of Insulin in Early Diabetes Mellitus; Walter L. Palmer, M.D., F.A.C.P., and W. Ricketts, M.D., guest, Chicago, Studies on the Effect of Roentgen Irradiation in Peptic Ulcer; R. H. Ebert, M.D., guest, J. J. Ahern, M.D., guest, and Robert G. Block,

M.D., F.A.C.P., Chicago, Development of Tuberculous Infection: In Vivo Observations in the Rabbit Ear Chamber; John B. Youmans, M.D., F.A.C.P., Chicago, The Nutritional Anemias in Practice; William D. Robinson, M.D., F.A.C.P., Ann Arbor, Nutritional Aspects of Rheumatoid Arthritis; J. R. McDonald, M.D., guest, Clinical Appraisal of Examination of the Sputum in Carcinoma of the Lung Aspects; J. L. Sims, M.D. (Associate), Madison, Wis., Pulmonary Adenomatosis, Its Clinical Diagnosis; R. M. Angle, M.D., guest, and Howard L. Alt, M.D., F.A.C.P., Chicago, Hepatitis without Jaundice in Infectious Mononucleosis; L. T. Iseri, M.D., A. J. Boyle, M.D., S. D. Jacobson, M.D., T. M. Batchelor, M.D., guests, and Gordon B. Myers, M.D., F.A.C.P., Detroit, Diagnosis of Uremia Due to Lower Nephron Nephrosis. Presiding officers included Dr. Frank J. Heck, F.A.C.P., Rochester, Minn., Dr. Karver L. Puestow, F.A.C.P., Madison, Governor for Wisconsin, Dr. Cecil M. Jack, F.A.C.P., Decatur, Governor for Southern Illinois, and Dr. Robert M. Moore, F.A.C.P., Indianapolis, Governor for Indiana. Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Regent, was Toastmaster in the evening. The distinguished guests included Edgar A. Guest, Detroit poet, Dr. Reginald Fitz, A.C.P. President-Elect, Dr. William S. Middleton, 1st Vice President, Dr. Ernest E. Irons, Regent, Dr. Walter L. Palmer, Chairman of the Board of Governors, and Mr. E. R. Loveland, Executive Secretary.

#### SPECIALTY BOARD NOTICES

AMERICAN BOARD OF INTERNAL MEDICINE, William A. Werrell, M.D., Asst. Secretary-Treasurer, 1 W. Main St., Madison 3, Wis. Oral examination at San Francisco on February 8, 9, and 10, 1949—closing date for acceptance of applications December 1, 1948. Oral at New York City on March 23, 24, and 25, 1949—closing date for acceptance of applications January 2, 1949. Oral at Philadelphia on June 1, 2, and 3, 1949—closing date for acceptance of applications January 2, 1949. Written examination on October 17, 1949—closing date for acceptance of applications May 1, 1949.

THE AMERICAN BOARD OF PEDIATRICS, INC., John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Rd., Rosemont, Pa. The next written examination will be held on January 7, 1949. Oral examinations are scheduled to be given at St. Louis, Mo., on February 18, 19 and 20, 1949, and at Baltimore, Md., on April 22, 23 and 24, 1949.

THE AMERICAN BOARD OF PHYSICAL MEDICINE, Robert L. Bennett, M.D., Secretary-Treasurer, 30 N. Michigan Ave., Chicago 2, Ill. The examination period will be two days immediately prior to the annual convention of the American Medical Association, June, 1949, at Atlantic City, N. J. Applications must be complete and in the hands of the Secretary-Treasurer three months prior to this date.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC., F. J. Braceland, M.D., Secretary-Treasurer, 102 2nd Ave., S.W., Rochester, Minn. The next semi-annual examination of candidates will be held during the annual meeting of the Board, at New York City, on December 12, 13, 14 and 15, 1948. The forms for this examination are closed, but forms are now open for the Spring examination which will be given during May, 1949. Exact dates and place will be announced later. All applications must be in the hands of the Secretary-Treasurer at least 90 days before the examination date.

THE AMERICAN BOARD OF RADIOLOGY, B. R. Kirklin, M.D., Secretary-Treasurer, 102 2nd Ave., S.W., Rochester, Minn. The next scheduled examination will be held at Haddon Hall, Atlantic City, N. J., May 31–June 4, 1949.

THE ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA, John E. Plunkett, M.D., Honorary Secretary, 150 Metcalfe St., Ottawa, Ont., Can. The

Annual Scientific Meeting of the College will be held at the Chateau Laurier Hotel, Ottawa, on November 26 and 27, 1948.

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The Medical Society of the State of Pennsylvania held its Centennial Celebration Session at Philadelphia, October 3-7, 1948, with Dr. Edward L. Bortz, F.A.C.P., as Chairman of the Celebration Committee. Members of the American College of Physicians who presented papers included Dr. Kenneth E. Quickel, F.A.C.P., Harrisburg; Drs. Joseph T. Beardwood, Jr., Julius H. Comroe, Jr., Charles E. Brown, A. Reynolds Crane, Herbert T. Kelly, David W. Kramer, T. Grier Miller, Ralph Pemberton, Hobart Reimann, Stanley Reimann, T. G. Schnabel, W. D. Stroud, Joseph B. Vander Veer and Edward Weiss, Fellows, and Dr. Peter A. Herbut, Associate, all of Philadelphia; Dr. R. R. Snowden, F.A.C.P., and Drs. Robert C. Grauer and George E. Martin, Associates, Pittsburgh; Dr. Eli Eichelberger, Associate, York; Louis Krause, M.D., F.A.C.P., and Dr. Maurice C. Pincoffs, M.A.C.P., Baltimore, Md.; Elmer C. Bartels, M.D., F.A.C.P., Boston, Mass.; Hans H. Reese, M.D., F.A.C.P., Madison, Wis.

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The Mississippi Valley Medical Society held its 13th Annual Meeting at Springfield, Ill., September 29-October 1, 1948. Dr. A. J. Carlson, M.A.C.P., Chicago, Dr. Arthur R. Colwell, F.A.C.P., Evanston, Ill., and Drs. L. T. Coggeshall, F.A.C.P., Paul S. Rhoads, F.A.C.P., Willard O. Thompson, F.A.C.P., and John B. Youmans, F.A.C.P., of Chicago, and Dr. R. O. Muether, F.A.C.P., St. Louis, were speakers.

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During the recent International Medical Assembly of the Inter-State Post-graduate Medical Association of North America, which met at Cleveland, Ohio, November 9-12, 1948, the following Fellows of the College were speakers: Drs. Irvine H. Page and Robert D. Taylor, Cleveland, Treatment of Hypertensive Disease; Dr. Mavis P. Kelsey, Rochester, Minn., Treatment of Exophthalmic Goiter with Radio-iodine; Dr. Howard A. Rusk, New York, N. Y., Dynamic Therapeutics in Chronic Disease; Dr. Tom D. Spies, Birmingham, Ala., Recent Progress in Nutrition; Dr. E. Perry McCullagh, Cleveland, Testicular Dysfunction; Dr. Edward L. Bortz, Philadelphia, Management of Elderly Patients; Dr. Ray F. Farquharson, Toronto, Extreme Insufficiency of the Anterior Lobe of the Pituitary Gland; Dr. Walter Freeman, Washington, D. C., Use of Prefrontal Lobotomy in the Treatment of Pain; Dr. Cyrus C. Sturgis, Ann Arbor, Mich., Clinic Illustrating Newer Methods in the Treatment of Hematologic Disorders; Dr. Hans H. Reese, Madison, Wis., Multiple Sclerosis; Dr. Philip Levine, Raritan, N. J., Practical Application of Isoimmunization by the Rh Factor; Dr. John H. Talbott, Buffalo, N. Y., Gouty Arthritis; Dr. W. Philip Corr, Riverside, Calif., Diagnosis and Treatment of Cirrhosis of the Liver.

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The Dallas Southern Clinical Society will hold its 1949 Annual Spring Clinical Conference on March 14-17. A. McGehee Harvey, M.D., F.A.C.P., Baltimore, Md., and Julian M. Ruffin, M.D., F.A.C.P., Durham, N. C., will be among the Honor Guest Speakers.

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Samuel M. Jacobson, M.D., F.A.C.P., Cumberland, Md., addressed the Somerset County, Pa., Medical Society on September 21, 1948, on the subject "Congenital Heart Disease."

The University of California Medical School will offer during 1949 the following postgraduate courses of interest to internists: Cardiology, January 31-February 4; Endocrinology, including Diabetes, June 20-24; Diseases of the Chest, December 5-9. Inquiries and applications may be addressed to Stacy R. Mettier, M.D., F.A.C.P., Head of Postgraduate Instruction, The Medical Center, San Francisco 22, Calif.

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#### DR. J. ROSCOE MILLER APPOINTED PRESIDENT OF NORTHWESTERN UNIVERSITY

The College has again been honored by the selection of one of its leading Fellows from Chicago for appointment to the presidency of an important university. In 1946 Dr. Raymond B. Allen, then Vice President of the University of Illinois, was elected President of the University of Washington. Recently, Dr. J. Roscoe Miller, Dean of Northwestern University Medical School since 1941, was appointed by the Board of Trustees of Northwestern University to succeed Dr. Franklyn Bliss Snyder as President of that institution on July 1, 1949.

Dr. Miller received the A.B. degree from the University of Utah in 1925, and the M.D. and M.S. degrees from Northwestern University in 1929 and 1931. Following internship at St. Luke's Hospital, Chicago, Dr. Miller became a member of the medical staffs of the Passavant and Wesley Memorial Hospitals. He was appointed Assistant Dean of the Northwestern University Medical School in 1933; Associate in Medicine, in 1937; Assistant Professor of Medicine, 1939; Dean and Associate Professor of Medicine, 1941. During the recent War, Dr. Miller served as Commander in the Medical Corps, U. S. Naval Reserve, as head of the Section on Internal Medicine in the Bureau of Medicine and Surgery, and he has since been appointed Consultant in Internal Medicine to the Surgeon General.

Dr. Miller is a diplomate of the American Board of Internal Medicine, in that specialty and in cardiovascular diseases. He was elected to Fellowship in the American College of Physicians in 1938.

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Dr. Thomas Parran, F.A.C.P., who recently retired from the U. S. Public Health Service to become Dean of The School of Public Health of the University of Pittsburgh, has been honored by the award of the Distinguished Service Medal.

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Pascal F. Lucchesi, M.D., F.A.C.P., Superintendent and Medical Director of the Philadelphia General Hospital, was recently selected for the award of the Dr. I. P. Strittmatter medal by the Philadelphia County Medical Society.

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It was recently announced that Dr. C. Sidney Burwell, F.A.C.P., will relinquish on February 1, 1949, the Deanship of Harvard Medical School. He will, however, continue his activities as Research Professor of Clinical Medicine in the School, and at the Peter Bent Brigham Hospital.

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Harold J. Harris, M.D., F.A.C.P., New York, N. Y., is a participant in The Second Inter-American Congress on Brucellosis at Mendoza, Argentina, November 17-22, and at Buenos Aires, November 22-26, with a paper on "Recent Advances in Diagnosis and Treatment of Chronic Brucellosis." Dr. Harris spoke before the Laboratory Section of the American Public Health Association, at the Annual Meeting in Boston on November 9, on "Chronic Brucellosis; The Unsatisfactory Status of Present Diagnostic Methods."

Dr. Karl Rothschild, F.A.C.P., New Brunswick, N. J., attended the International Congress on Mental Hygiene in London, England, August 16-21, 1948, as a delegate of the New Jersey Neuro-Psychiatric Association. He presented a short paper on the program.

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#### GIFT TO THE COLLEGE LIBRARY OF PUBLICATIONS BY MEMBERS

Dr. William Gerry Morgan, M.A.C.P., Washington, D. C., has presented to the Library of the American College of Physicians a bound volume of all of his medical articles published since 1930, comprising a book of some formidable size. In autographing his gift to the Library, he added "presented to the Library of the American College of Physicians, not in the belief that anything in this volume has any special merit, but in the hope that it may stimulate other Fellows to do likewise." Dr. Morgan is one of the charter members of the American College of Physicians, served many years on its Board of Regents and on its Board of Governors and was at one time the Secretary General of the College.

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#### MEDICAL SOCIETY EXECUTIVES CONFERENCE

The Medical Society Executives Conference is an Association of executive employees of national, state, regional and county medical societies, whose purposes are to enable medical society executives to improve the quality and efficiency of their services to their respective societies and to the medical profession generally; to provide a mechanism for the exchange of information and experience among medical society executives, for mutual improvement and for Fellowship.

The Conference was formally organized in 1947 and has held annual meetings since then. It numbers more than 120 members, including the vast majority of all eligible executive employees of recognized medical societies throughout the United States.

## OBITUARIES

## DR. EDMOND ELMORE BOHLENDER

Dr. Edmond Elmore Bohlender (Associate), Dayton, Ohio, died April 26, 1948, aged 80. He was a graduate of the Medical College of Ohio, 1894, was engaged in general medical practice, and for many years was a medical examiner for the Metropolitan Life Insurance Company. He became an Associate of the American College of Physicians by virtue of membership (1925) in the American Congress on Internal Medicine, an organization that was merged with the College in 1926, its members being automatically made Associates of the College at that time.

## DR. WARREN COLEMAN

Dr. Warren Coleman, a native of Augusta, Ga., died there February 13, 1948, at the age of 79. The major part of his professional life was spent in New York City where he held appointment as Professor of Clinical Medicine and Applied Pharmacology in the Cornell University Medical College, 1909-18, and as Assistant Professor of Medicine, Professor of Clinical Medicine, and Professor Emeritus of Clinical Medicine, after 1918.

Dr. Coleman was a graduate of Transylvania College, from which he later received an Honorary A.M. degree. He obtained his M.D. degree from the New York University College of Medicine in 1891 and later took postgraduate studies at the Johns Hopkins University School of Medicine. During his long practice in New York, he achieved eminence through the innovations in diet in treatment of typhoid fever which he advocated. The reports of results which he had obtained from the use of full diet for typhoid patients led to their feeding rather than starving as had been previously customary. He served for many years on the staffs of the New York City Hospital, Lenox Hill Hospital, Bellevue Hospital, and shortly before his death he received a medal and citation, "for distinguished and exceptional public service," from the Commissioner of Hospitals of New York City. In 1938, Dr. Coleman returned to Augusta and accepted appointment as Professor of Clinical Medicine in the University of Georgia School of Medicine. He resigned this appointment in 1939 following a heart attack.

Dr. Coleman published many important and excellent papers during his long career, chiefly devoted to the subject of physical diagnosis. He was especially interested in the development of the sense of palpation and vibratory sense in physical examination. A master clinician, he delighted in teaching medical students the art of true physical diagnosis dependent upon the use of the five senses. A modest and unpretentious though eminent physician, Dr. Coleman took active interest in politics in Augusta and was instrumental in organizing the Citizen's Union and was a strong backer of the Independent Party. It is said that he served as the model for Colonel Effingham in the book, "Colonel Effingham's Raid."

CARTER SMITH, M.D., F.A.C.P.,  
Governor for Georgia

## DR. WILLARD D. KLINE

Willard Daniel Kline, M.D., was a favorite among his colleagues, and will be greatly missed. He was born in Allentown, Pa., on July 4, 1877, and died August 9, 1948.

Dr. Kline went to Muhlenberg College and obtained his B.A. degree in 1897. He took his medical training at Jefferson Medical College of Philadelphia, and received

his M.D. degree in 1901, subsequently serving his internship at The Lankenau Hospital, Philadelphia, where he received surgical training under the famed surgeon, John B. Deaver, M.D.

During the years 1905 to 1922, Dr. Kline was Physician to Muhlenberg College. From 1912 to 1920, he was Chief, State Tuberculosis Dispensary, and from 1920 to 1922, chest examiner, United States Veterans Bureau. Dr. Kline became Staff Physician to the Sacred Heart Hospital, Allentown, in 1916, and became Dean of its Medical Division in 1934.

Our friend is a past president of the Lehigh County Medical Society, and served as treasurer for a period of fifteen years.

Dr. Kline was a Fellow of the American Medical Association and became a Fellow of the American College of Physicians in December, 1939.

Dr. Kline's genial and kindly disposition will be missed by a host of friends, both in and out of the medical profession.

EDWARD L. BORTZ, M.D., F.A.C.P.,  
Governor for Eastern Pennsylvania

### DR. SOLOMON SOLIS-COHEN

Dr. Solomon Solis-Cohen, the oldest living member of a family prominent in the life of Philadelphia since before the Revolution, died July 12, 1948, at the age of 90. He was an unusually gifted teacher, a sincere, honest, and devoted physician, and a zealous worker in many fields, in which he published actively.

Dr. Solis-Cohen received his Bachelor and Master of Arts degrees from Central High School, the M.D. and D.Sc. degrees from Jefferson Medical College of Philadelphia, D.H.L. from the Jewish Theological Seminary of America, and D.Sc. from the Philadelphia College of Pharmacy and Science. He began his career in the Out-Patient Department of the Jefferson Medical College Hospital in 1884 as Chief Clinical Assistant of that department. His first appointment to the faculty of the Jefferson Medical College of Philadelphia was in 1885 as Lecturer on Special Therapeutics. He became Assistant Professor of Medicine in 1902, Professor of Clinical Medicine, 1904, and served in the latter capacity until 1928 when he was appointed Emeritus Professor of Clinical Medicine. Dr. Solis-Cohen was also Consulting Physician to the Philadelphia General and Jewish Hospitals.

Dr. Solis-Cohen was a member of the Philadelphia County Medical Society, Medical Society of the State of Pennsylvania, the Pathological Society of Philadelphia, an Honorary Member of the Medical and Chirurgical Faculty of Maryland, the Lehigh Valley, Tri-State, and St. Louis Medical Societies. A Fellow of the American Medical Association, the Association of American Physicians, and the College of Physicians of Philadelphia, he was elected to Fellowship in the American College of Physicians in 1923.

Our Doctor was distinguished in many fields. He was among the first Americans, if not actually the first, to advocate the hydrotherapeutic management of typhoid fever. He was a Hebrew scholar and at times active in support of Zionist, and later non-Zionist, interests and in political affairs. He had a keen interest in music, and poetry was his hobby. John Greenleaf Whittier reprinted the famous, "I Know My Redeemer Liveth," in his anthology, "Songs of Three Centuries."

The passing of such a distinguished man will be a great loss to his friends and associates.

EDWARD L. BORTZ, M.D., F.A.C.P.,  
Governor for Eastern Pennsylvania

## DR. WILLIAM PAYNE THOMPSON

Dr. William Payne Thompson, F.A.C.P., of Princeton, N.J., died suddenly August 10, 1948, at the New York Hospital, of a massive acute hemorrhage from a peptic ulcer.

Dr. Thompson was born April 16, 1897, in Tuxedo Park, N. Y. He prepared for and entered Yale, and in World War I was a member of the first Naval aviation unit organized at Yale. He subsequently transferred to Columbia University, N. Y., where he was graduated Bachelor of Science in 1921, and Doctor of Medicine in 1924. He interned at the Presbyterian Hospital, N. Y., 1924-26, and was Resident in Pathology and Assistant in Medicine at Johns Hopkins, 1926-28. Dr. Thompson served the Columbia University College of Physicians and Surgeons as Instructor in Medicine, Associate in Medicine and Assistant Professor of Medicine, successively. For a number of years he was Assistant Attending Physician at the Presbyterian Hospital.

In 1946 Dr. Thompson moved to Princeton, where he took an interest in New Jersey medicine and was made President of the Board of Managers, New Jersey State Hospital at Marlboro, member of the Staff of Mercer Hospital, Trenton, and Consultant in Medicine, Fitkin Memorial Hospital, Neptune. He was also Secretary of the Board of Trustees of Trudeau Sanatorium. He was a Fellow of the New York Academy of Medicine, former Treasurer of the American Society for Clinical Investigation, and a Fellow of the American College of Physicians since 1940.

Dr. Thompson was especially distinguished in the field of hematology and for his studies on disorders of the spleen. Among his significant medical contributions are his descriptions of tuberculous pericarditis in the aged; the experimental production of portal hypertension, calling attention to its relationship to splenic hypertrophy and the secondary effects on activity of the bone marrow; and his correlations between the blood picture in so-called aplastic anemia and bone marrow patterns. He was one of the founders of the Spleen Clinic at the Presbyterian Hospital, where, for the first time, internists, surgeons, hematologists and pathologists were joined in a group to study splenic diseases.

He was an enthusiastic and inspiring teacher, a keen and discerning internist, and a most efficient organizer of clinical material. For the past several years he was the victim of chronic ill health, yet he maintained to the point of his endurance a sincere devotion to his many fields of interest and gave much of this time and energy to philanthropic causes and worthy institutions. His numerous associates and friends deplore deeply his untimely passing.

FRANKLIN M. HANGER, M.D., F.A.C.P.

## DR. HARLEY A. WILLIAMS

Dr. Harley A. Williams was born in Huron County, Ohio, on November 18, 1900, and died in Cleveland, March 5, 1948.

He received his A.B. degree from Oberlin College in 1923; his A.M. degree from the same school in 1925; and his M.D. in 1929 from Western Reserve University School of Medicine, where he stood at the head of his class and was honored by election to AOA. Dr. Williams interned and served as Assistant Resident in Medicine in the Lakeside Hospital, Cleveland, from 1929 to 1931. He joined the Faculty of the Western Reserve University School of Medicine in 1931 as Assistant Physician, advancing to Associate Physician and, ultimately, to the position of Physician-in-Charge of the Outpatient Department. In 1938 he was made Assistant Clinical Professor of Medicine. He was always fascinated by the possibilities presented in the teaching of physical diagnosis and was in charge of this course for a number of



years. Dr. Williams became a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians in 1937. He was active in the affairs of the Cleveland Academy of Medicine, serving on its Board of Trustees, and as Vice President in 1941.

As a house officer, Dr. Williams showed considerable curiosity, and, in addition to several brief clinical reports, showed that bovine was as effective as human gastric juice in producing remissions in pernicious anemia. But his love of people and of the immediate practice of medicine was too strong to permit him to yield to the intellectual satisfaction of an academic career. Because of his devotion to his patients, combined with exceptional diagnostic skill, his practice grew rapidly. He was much sought after as a consultant by younger men in his own city and in the surrounding counties. These calls he accepted eagerly and enthusiastically, both because of the challenge to his diagnostic skill and the opportunity it gave him to be of help to a collegue. He served as a good teacher in this role, as he did on the wards and in the Outpatient Department of the Lakeside Hospital. His chief interests aside from his profession and his family were the occasional hunting and fishing vacations which he enjoyed.

The sudden and untimely termination of the services to his community of this fine physician is deeply regretted by his numerous friends, students, and patients.

CHARLES A. DOAN, M.D., F.A.C.P.,  
Governor for Ohio

#### DR. HENRY LEWIS COOPER

Dr. Henry Lewis Cooper was born in Philadelphia, Pa., on February 28, 1897. He was educated in Colorado, where he attended the University of Denver and obtained his medical degree from the University of Colorado School of Medicine in 1920. His internship was served at St. Luke's Hospital, Denver. All of Dr. Cooper's professional life took place in Colorado, and he became one of the outstanding internists and citizens of the region. He died suddenly on June 23, 1948.

Dr. Cooper's professional and civic activities were many and varied. At the time of his death, he was Assistant Professor of Medicine in the University of Colorado School of Medicine. He was active on the staffs of the Colorado General, Denver General, and Mercy Hospitals. He served for a great many years on the Medical Advisory Board of the National Jewish Hospital, and was Vice Chairman of the Board at the time of his death. He saw strenuous activity during World War II as a Major and Lieutenant Colonel in the Medical Corps, Army of the United States, attached to the Army Air Forces. Dr. Cooper became a Fellow of the American College of Physicians in 1940, and was an active member of the Denver County, Colorado State and American Medical Associations.

WARD DARLEY, M.D., F.A.C.P.,  
Governor for Colorado

#### DR. PHILLIP HALLOCK

Dr. Phillip Hallock was born February 28, 1903, at Superior, Wis., and died in Los Angeles, June 29, 1948.

He attended the University of Minnesota, having been graduated from the medical school in 1929. He received his Master of Science degree in 1934. In 1936 he did postgraduate work in Amsterdam and London. From 1937 to 1940 Dr. Hallock was an Instructor in Medicine in the University of Minnesota Medical School, and was made Assistant Professor in 1940. During World War II, he served in the Medical Corps, Army of the United States, from February, 1942, to January, 1946,

and was discharged with rank of Lieutenant Colonel. Dr. Hallock subsequently established residence and practice in Los Angeles.

Dr. Hallock was a member of the Los Angeles County Medical Association, the Hennepin County and Minnesota State Medical Societies, Minnesota Society of Internal Medicine, Central Society of Clinical Research, American Heart Association, American Association for the Advancement of Science, American Society for Clinical Investigation; he was a Fellow of the American Medical Association, and, in 1940, became a Fellow of the American College of Physicians.

Dr. Hallock was respected and admired by his fellow practitioners. A great deal of his time was devoted to consultations at local Veterans Hospitals in this vicinity.

LELAND HAWKINS, M.D., F.A.C.P.,

Governor for Southern California

### DR. LAWTON M. HARTMAN, JR.

Dr. Lawton Mervale Hartman died October 6 at his home in York, Pa., after a long illness, following a cerebral hemorrhage. He was 69 years old.

Dr. Hartman attended the York Collegiate Institute and obtained the M.D. degree from the University of Pennsylvania School of Medicine in 1902. After an internship at Howard Hospital, Philadelphia, he returned to York and served three years at the York Hospital as interne. In 1906 he went to Europe, spending a year and a half in travel and medical study in Vienna. In 1907 he was appointed to the York Hospital medical staff and for 16 years was chief of its cardiovascular service. He also served for 18 years on the visiting staff of the Children's Home. During World War I he volunteered for service and was commissioned a captain in the Medical Reserve Corps. Since then he continued the practice of medicine in York.

Dr. Hartman was a life Fellow of the American College of Physicians, a Fellow of the American Medical Association, a member of the Medical Society of the State of Pennsylvania, the American Heart Association, and the York County Medical Society, whose president he was in 1911.

Dr. Hartman was an intense and profound student of medicine, especially interested in diseases of the cardiovascular system. As a diagnostician and consultant, he enjoyed a well earned reputation in York County and vicinity. Gifted with a friendly, sympathetic personality, he was able to achieve much in his career that scientific medicine alone would scarcely have accomplished. Modest and self-sacrificing, he was entirely devoted to family, friends, colleagues and patients, and he will long be remembered by all of them as a most thoughtful, studious physician whose decisions were made only after most thorough investigation and careful deliberation.

JULIUS H. COMROE, SR., M.D., F.A.C.P.

### DR. WILLIAM WILLIAMSON JARRELL

William Williamson Jarrell, M.D., F.A.C.P., was born in Cartersville, Ga., September 22, 1876. He died in Thomasville, Ga., June 21, 1948, from prostatic hypertrophy, complicated by chronic nephritis and uremia. He received his A.B. degree from Emory College in 1897 and was graduated from the Vanderbilt University School of Medicine in 1901. Dr. Jarrell took postgraduate work at the New York Polyclinic Medical School and Hospital and the Harvard Medical School.

Dr. Jarrell served in World War I as a major in the Medical Reserve Corps. He was a member of the senior medical staff of the John D. Archbold Memorial Hospital and was especially interested in cardiovascular-renal disease.

Dr. Jarrell was a member of the Thomas County Medical Society, the Second District Medical Society, the Medical Association of Georgia, and the Southern Medical Association, a Fellow of the American Medical Association and, since 1929, a

Fellow of the American College of Physicians. In his death the community lost a capable physician on whom countless people depended.

CARTER SMITH, M.D., F.A.C.P.,  
Governor for Georgia

### DR. OZA J. LABARGE

Dr. Oza Joseph LaBarge, Chief of Medical Service of the Veterans Administration Hospital, Alexandria, La., died July 28, 1948. Dr. LaBarge had been a Fellow of the American College of Physicians since 1932.

Born March 30, 1898, at Standish, Mich., Dr. LaBarge received his premedical and medical training at the University of Michigan, where he obtained the B.S. degree in 1921 and the M.D. in 1923. He subsequently engaged in the practice of medicine in Salt Lake City, where he held appointments as Instructor in Medicine in the University of Utah School of Medicine, as Junior in Medicine at the Latter Day Saints Hospital and as Senior Internist for the Union Pacific Railroad Company. Dr. LaBarge entered the Army in 1940 with rank of Lieutenant Colonel, and was assigned to the Station Hospital, Camp Livingston, La., where he served as Chief of Medical Service until July 12, 1944. He was then assigned to the 179th General Hospital as Chief of Medical Service, and was later appointed its Commanding Officer, with rank of Colonel. This Hospital was assigned to the European Theatre of Operations with station in the United Kingdom. Dr. LaBarge was separated from the service in May, 1946, and soon thereafter accepted his first assignment in the Veterans Administration as Chief Medical Officer of the Regional Office in Lubbock, Tex.

Dr. LaBarge was a diplomate of the American Board of Internal Medicine, a member of the Salt Lake County, Utah State and Pacific Northwest Medical Associations, of the Pacific Association of Railway Surgeons and the American Heart Association, and a Fellow of the American Medical Association.

### COLONEL CHARLES W. SALE, (M.C.), U.S.A., Ret'd

Colonel Charles Wallace Sale, Medical Corps, U. S. Army, Retired, died July 10, 1948, at Fredericksburg, Va., as the result of a cerebral hemorrhage.

He was born March 25, 1885, in Sealston, Va.; received his M.D. degree in 1907 from the University College of Medicine (Richmond); interned at the Retreat for the Sick, in Richmond, and was commissioned a First Lieutenant, Medical Corps, Regular Army, September 10, 1917, after serving a little more than three years in the Medical Reserve Corps.

During the First World War he served with the American Expeditionary Forces in France. After a short assignment in a General Hospital at Hampton, Va., he completed the course at the Army Medical School, Army Medical Center, Washington, D. C., and the indoctrination course at Medical Field Service School, Carlisle Barracks, Pa., and then was transferred to Camp Holabird, Md. In October, 1922, he became a Professor of Military Science and Tactics at the Medical College of Virginia, Richmond, and during his two years there did an excellent job. At three different times in his career he was stationed in the Philippines. Other short-term assignments include Army and Navy General Hospital, Hot Springs, Ark.; Fort Sill, Okla.; Fort Humphreys, Va.; and Fort Banks, N. Y. From March, 1941, until December, 1945, he performed duties of Chief of the Medical and Professional Services at Stark General Hospital, Charleston, S. C., and was very highly respected at that station. He was retired from service on May 31, 1946, with rank of Colonel.

CLIFFORD G. BLITCH, F.A.C.P.,  
Colonel, (M.C.), U. S. Army

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—Bockus, H. L.: Gastro-Entrology,  
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Company, 1944, Vol. 2, p. 533

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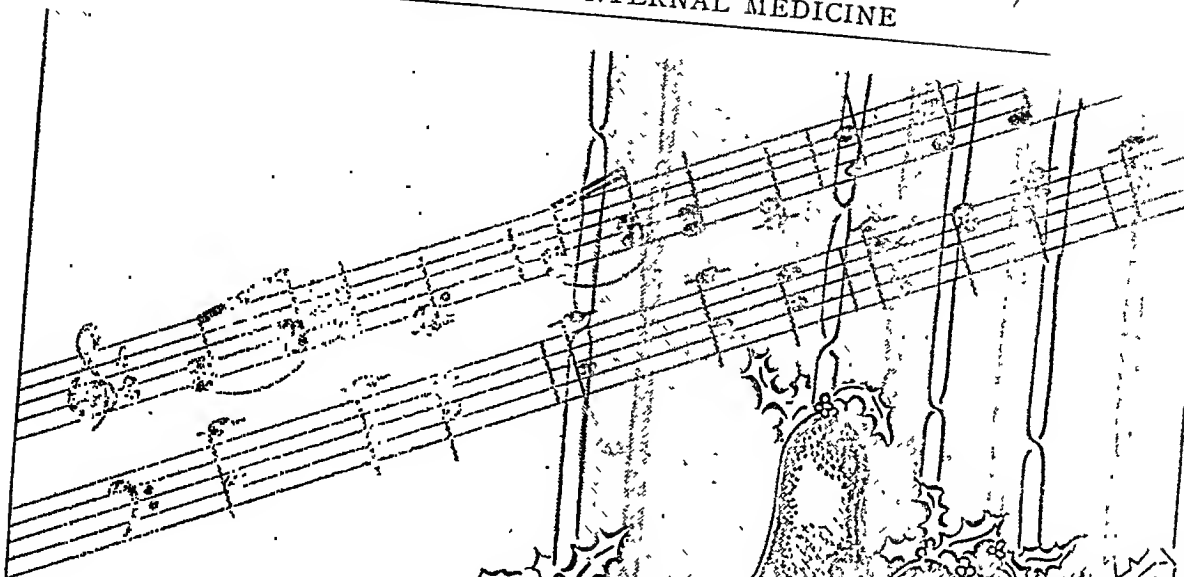
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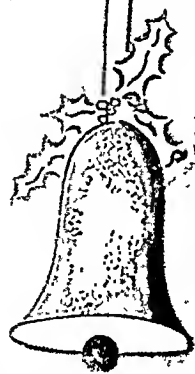
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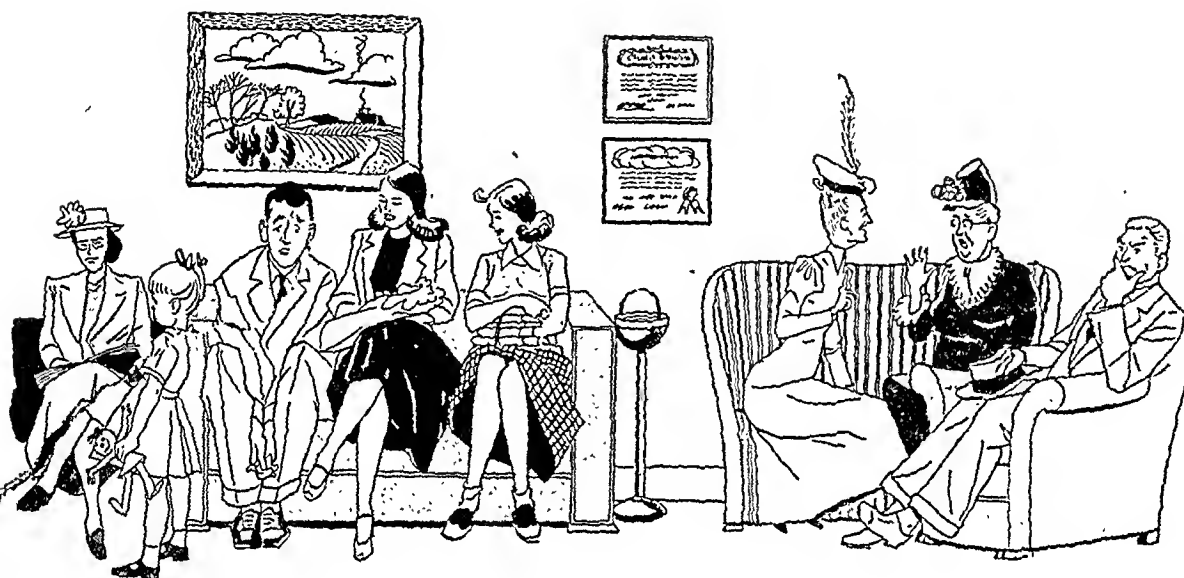
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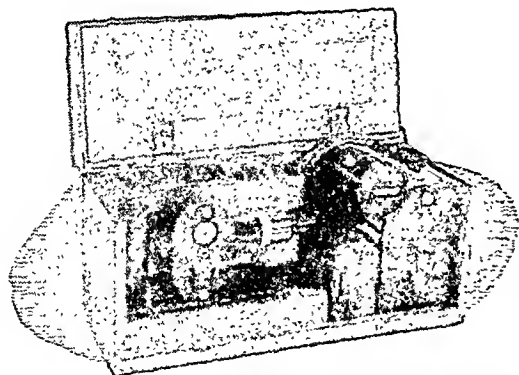
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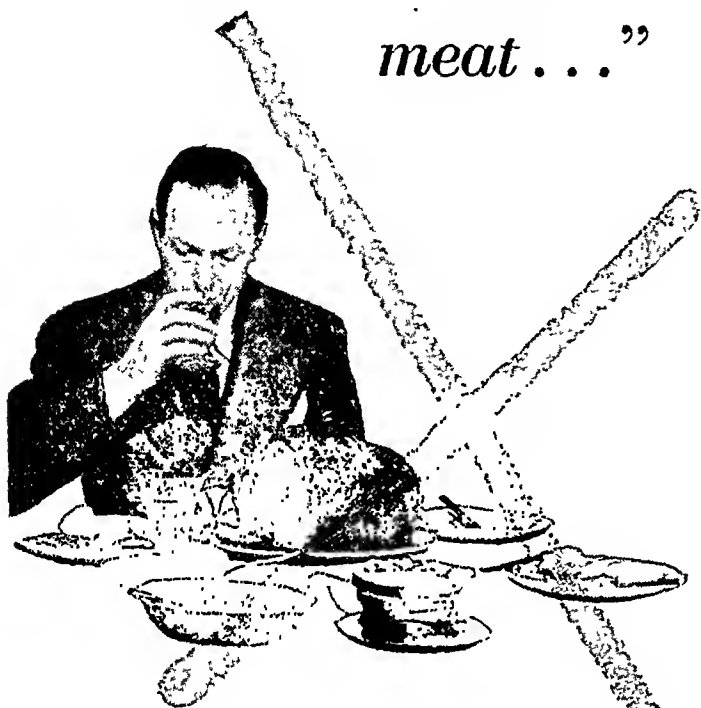
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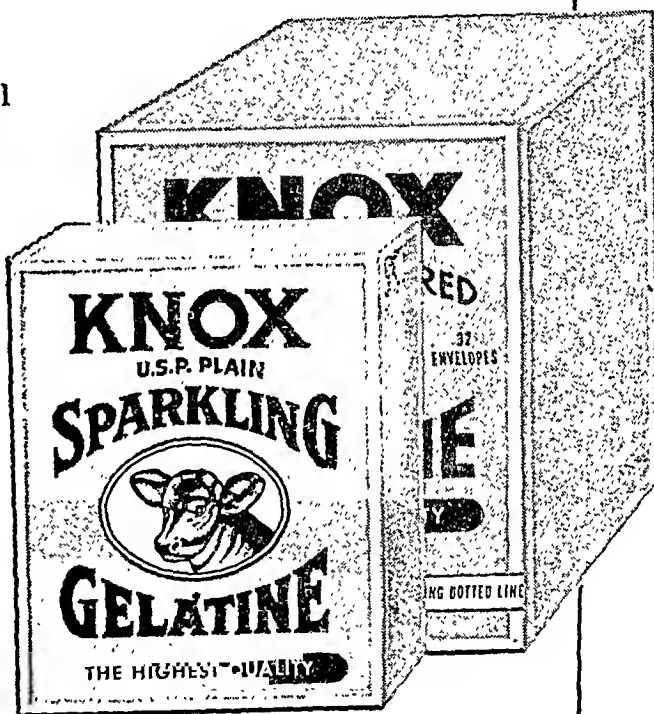
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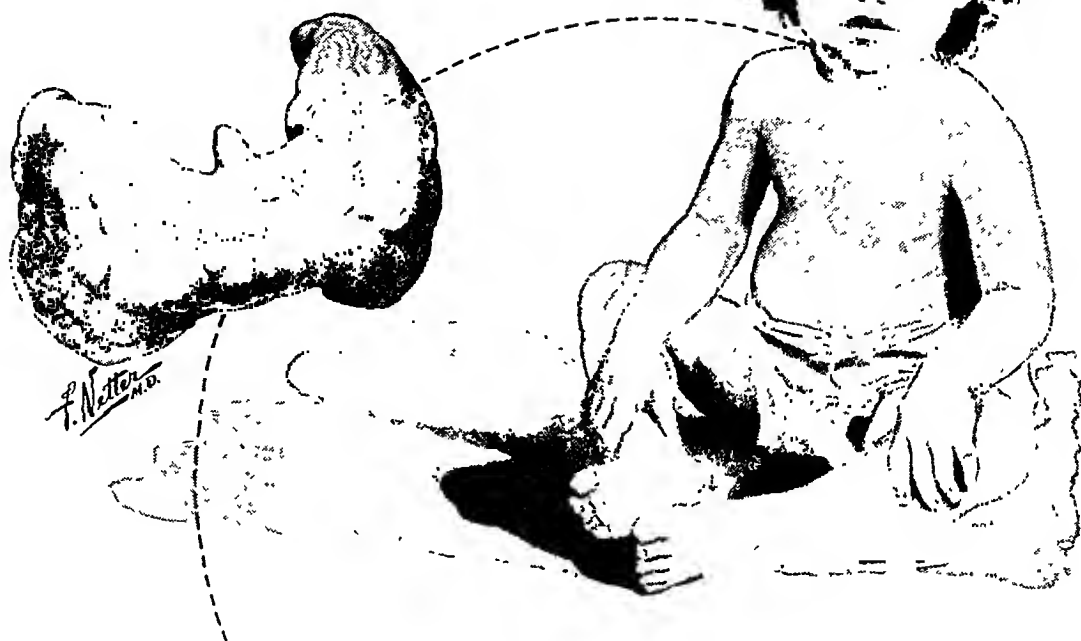
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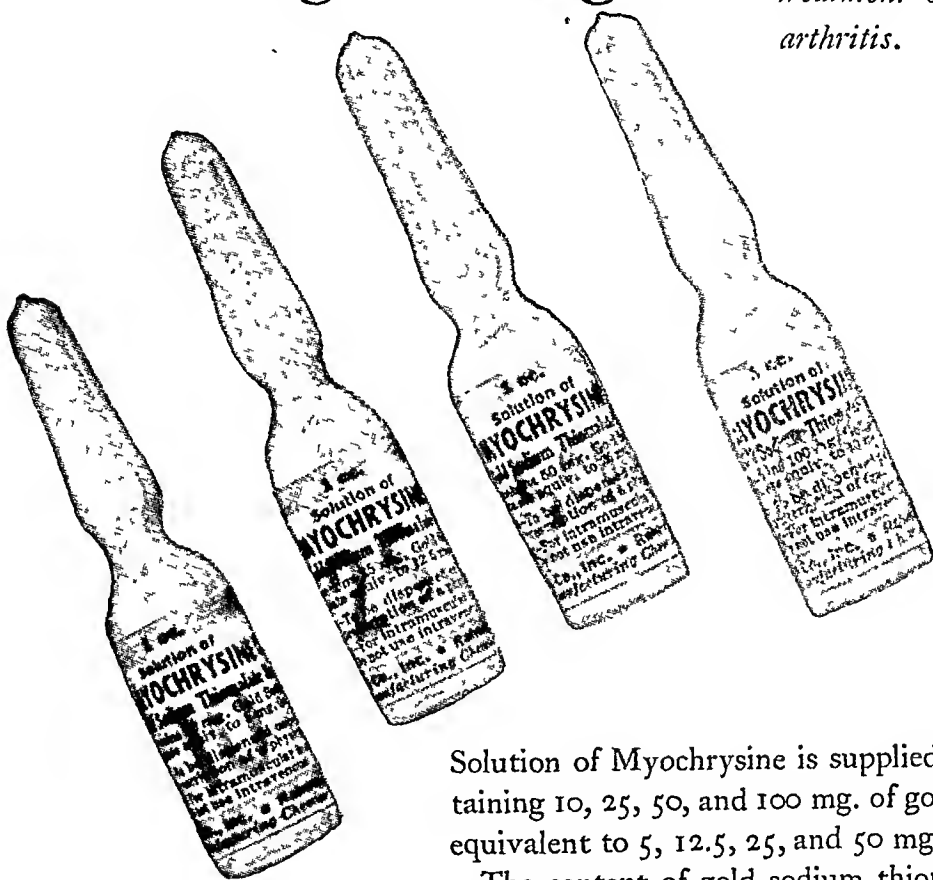
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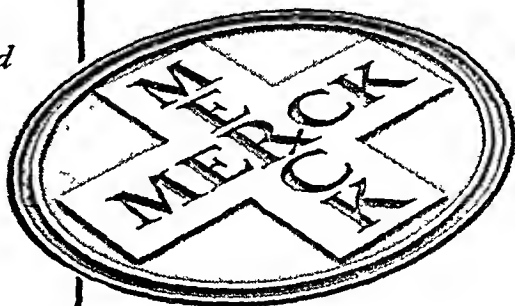
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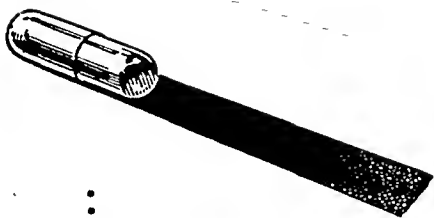
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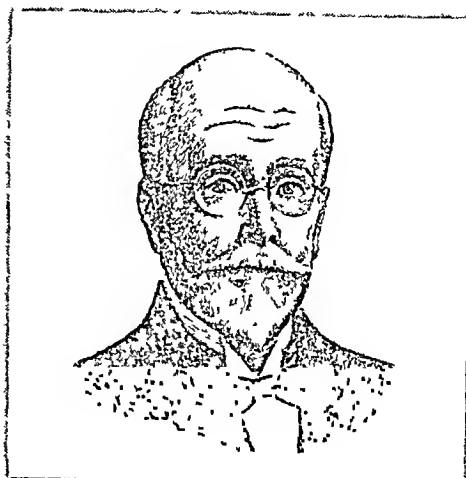
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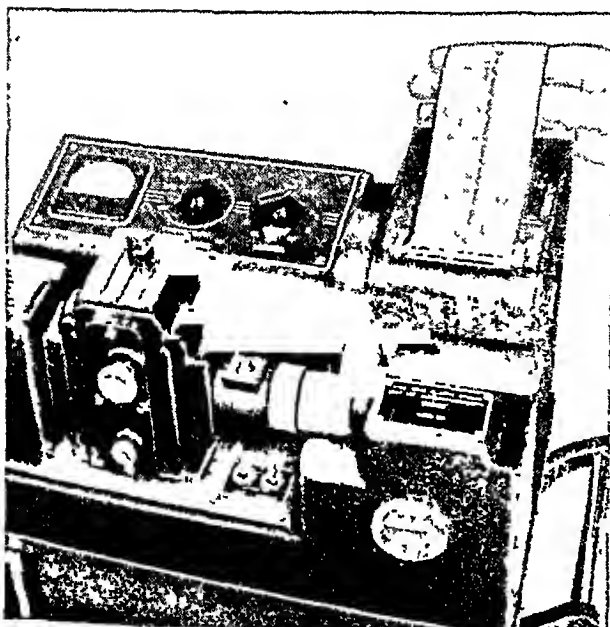
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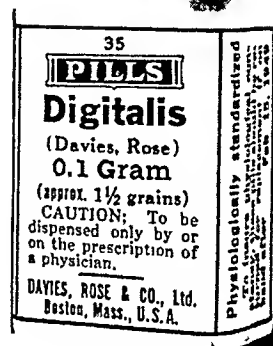
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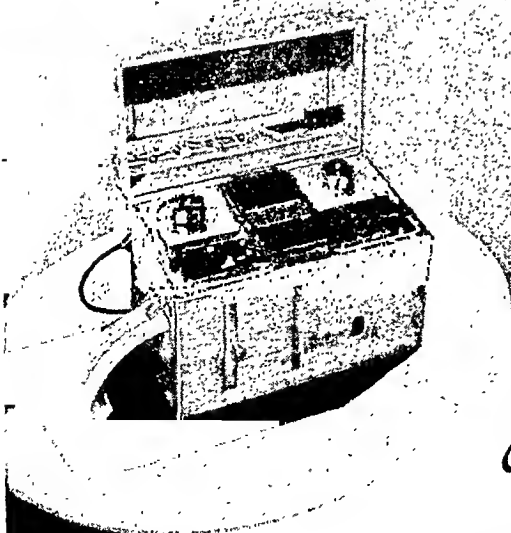
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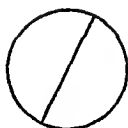
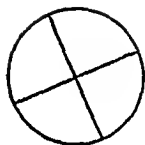


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1. New York State J. Med. 47:1003

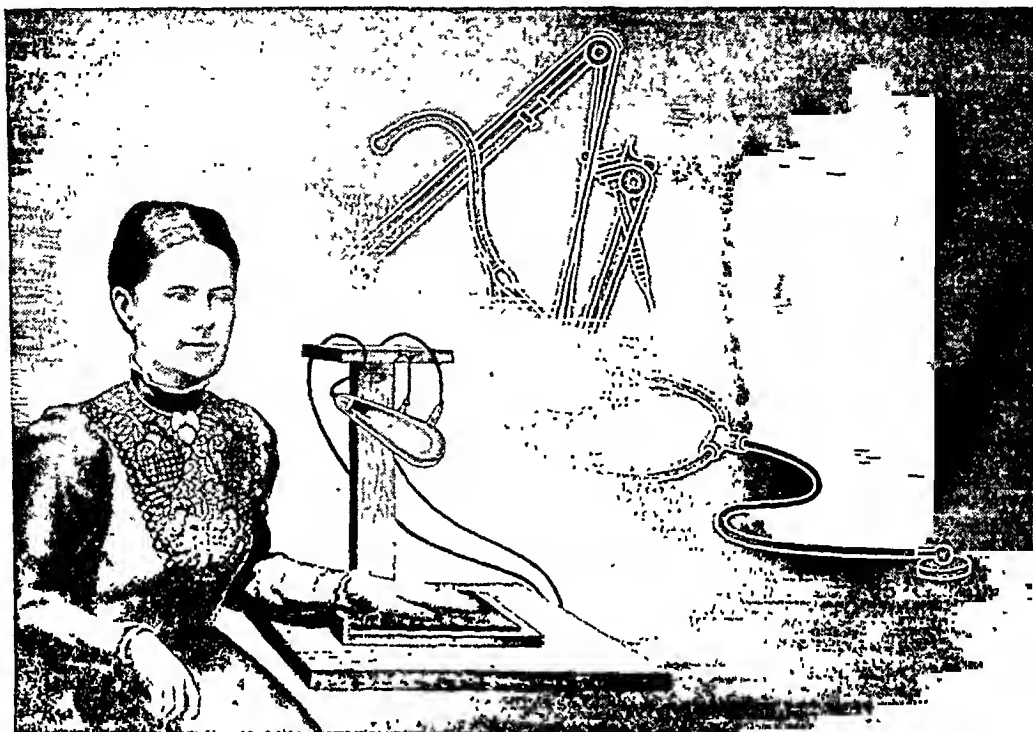
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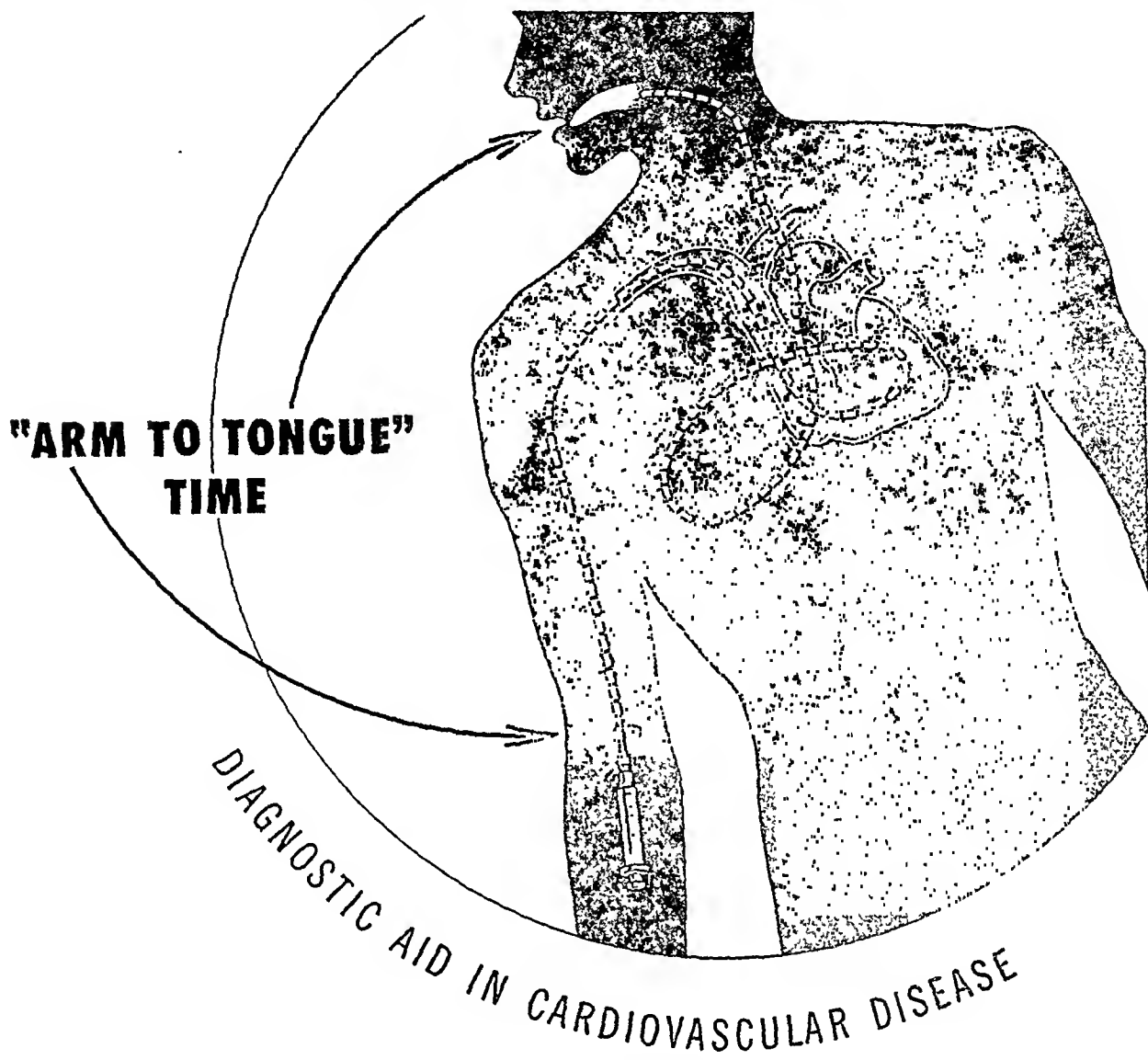
Further investigation disclosed its great penetrative and photographic powers. His first photograph recorded the bones of Frau Röntgen's hand. A "preliminary communication" on

his discovery was released on December 28, 1895, to the president of the Physical Medical Society of Würzburg—and the X-ray, so named by Röntgen for want of anything more definitive, was promptly welcomed in medical and dental circles.

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\*Hussey, H. H. and Katz, S.: Am. J. M. Sc., 201:669 (May) 1941.

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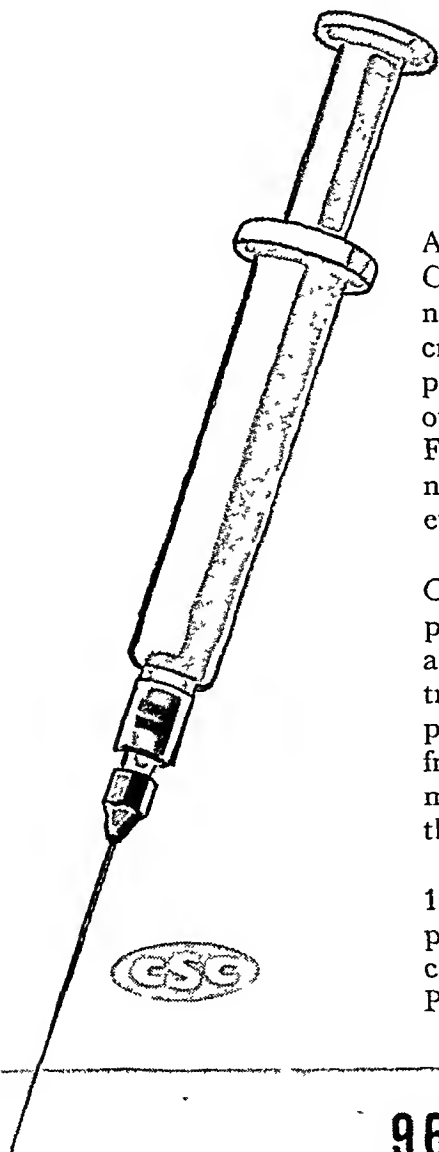


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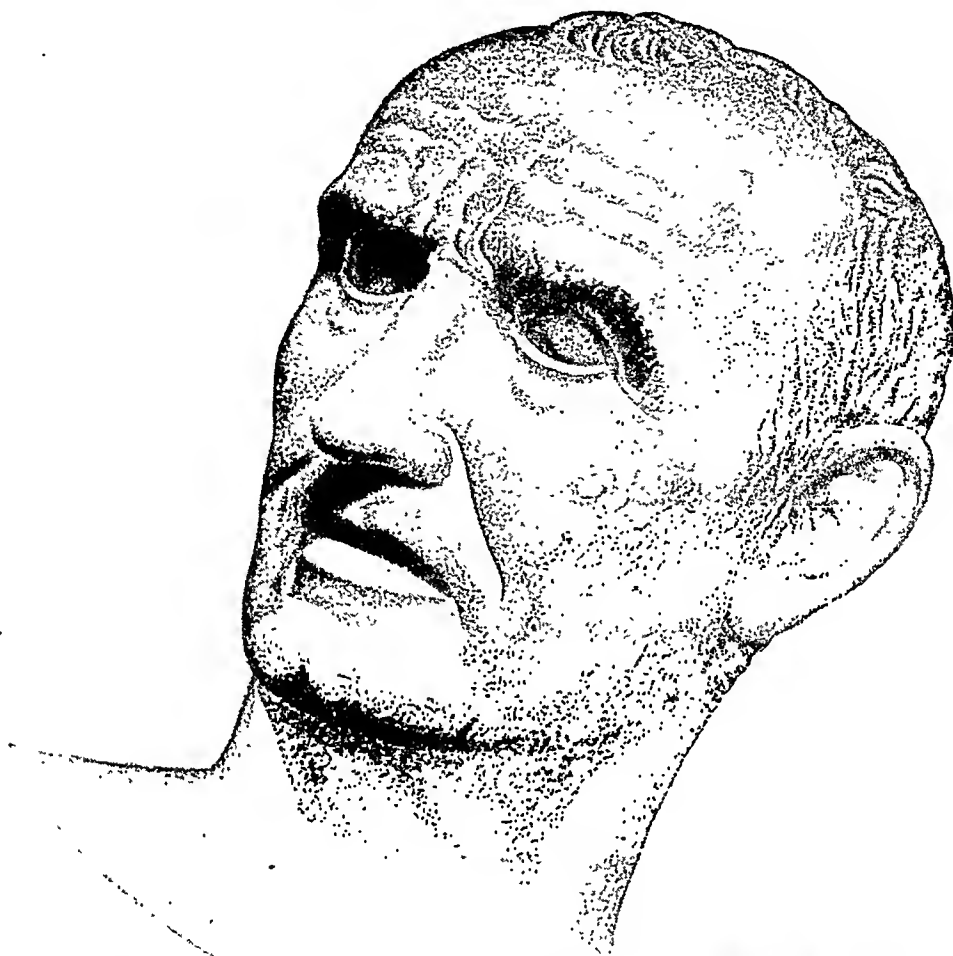
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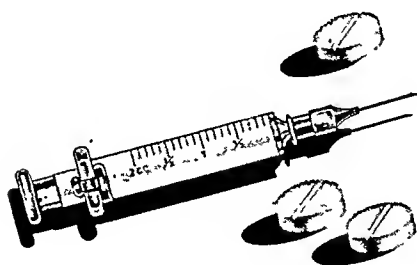
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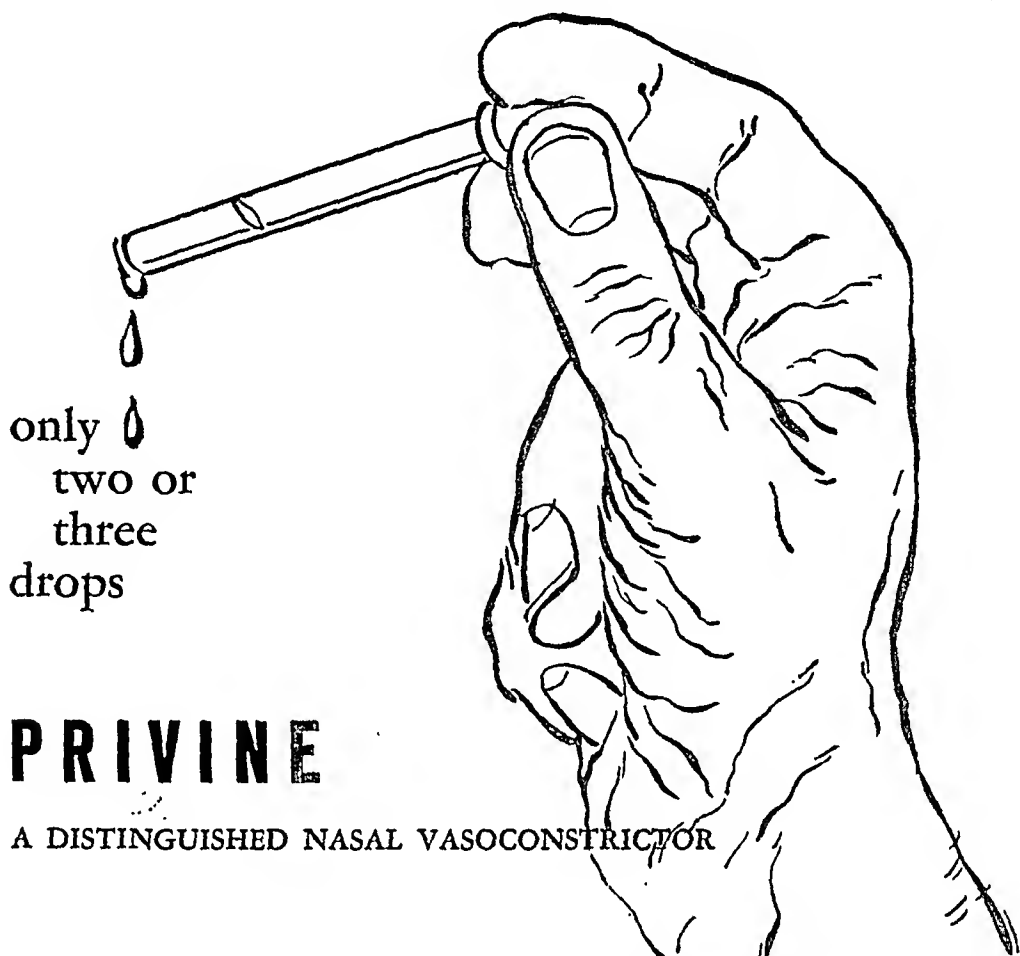


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# ANNALS OF INTERNAL MEDICINE

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VOLUME 29

DECEMBER, 1948

NUMBER 6

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## THE INTRACELLULAR ENVIRONMENT FOR INFECTIOUS AGENTS \*

By ERNEST W. GOODPASTURE, M.D., *Nashville, Tenn.*

THE John Phillips Award was established in 1929 to honor the memory of a distinguished and beloved member of this College. Originally designed as a Fellowship, it was changed in 1934 to its present form which includes the John Phillips Award Lecture. It is very gratifying to me to be the recipient of the honor of addressing you today under the auspices of this Award. I am pleased to do so in order to make a sincere though small contribution to the memory of your former esteemed colleague, and to join the roster of medical scientists who have paid their tribute to him on similar occasions.

The Board of Regents by establishing the John Phillips Memorial Award expressed the interest of the College in scientific research as a fundamental factor in the development of Medicine. It has seemed to me proper therefore to indicate in this lecture my preoccupation for many years with problems of infection, especially those bearing upon pathogenesis and more specifically concerning host-parasite relations in infection caused by agents thus far uncultivable. These agents seem to require an intimate relation with individual cells of the host in order to survive, to multiply and incidentally to cause disease.

Many common infectious diseases are caused by familiar microorganisms like the pyogenic cocci and certain bacilli that can be easily cultivated in the test tube on dead media. These parasites can be identified by the pathologist in their respective lesions such as a boil, a cellulitis, a pneumonia or meningitis; and it is observed that they invade the host and multiply in various tissue fluids outside the cells. Because of their easy in vitro culture and their identification by means of the light microscope, this group of infectious agents has received a great deal of attention by bacteriologists, immunologists and pathologists, with the result that our general ideas of infection are

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\* The John Phillips Memorial Lecture delivered at the Annual Meeting of the American College of Physicians, San Francisco, California, April 21, 1948.

From the Department of Pathology, Vanderbilt University, Nashville, Tenn.



based largely upon knowledge gained from assiduous examination of them. Nevertheless these extracellular, cultivable microbes probably are considerably in the minority among parasitic agents in general, for there is a multitude of infectious diseases from which it has thus far been impossible to cultivate an etiological agent on lifeless media although the respective parasites in general can be seen, or have been identified in other ways, as occupants of living cells of the host.<sup>1</sup>

If the pathologist could magnify a patient, animal or plant, invaded by one of these uncultivable intracellular parasites, to the extent that he could observe the ultimate beginnings of infection, he would be able to witness a series of remarkable biological events associated with the state of obligate intracellular parasitism. First he would observe the attachment of a parasitic cell or unit to the surface of some active functioning cell of the host. The parasitic unit would be seen to penetrate the surface of the cell so as to gain admission into the protoplasm itself. Within this internal *milieu* some would multiply and remain confined to the cytoplasm, dispersed or in aggregations. In other cases, however, the original unit or early multiples of it would, by movements of cytoplasmic fluid, reach the nucleus, and in due course would penetrate its surface to become embedded in or suspended by the nucleoplasm. Here in some types of infection the parasitic particles would be seen to multiply within the nuclear sap and to induce changes there easily visible with the light microscope. If the parasites remain and multiply only in the cytoplasm, each assumes a pattern of growth with respect to the structure of the cell that may be quite characteristic and perhaps indicative of the presence of local conditions in protoplasm exclusively adaptable to its needs.

The multiplication of parasitic units in cytoplasm or nucleus would be accompanied by a strange variety of imbalances in the normal energies of the cell, expressing themselves in observable gross results, such as mitosis, structural abnormalities or necrosis. The multiplication of these effects and their chains of sequelae would culminate in the symptoms and signs of one or another of the specific infections.

With knowledge at hand, and in the expansive era in which we find ourselves, it is not difficult to imagine such an enlarged picture of what has now become accepted as representative of the gross aspects of cell-parasite relationship in certain infectious diseases. But the light microscope fails us when we would seek to discern the intimacies and intricacies of interactions that transpire within the infected cell. If there were no hope of other instrumentalities and methods of following these events the observations which I wish to bring to your notice in this lecture would have of themselves little of interest.

It is my purpose to point out in instances of intracellular parasitism some observable relations of host-cell and invader that might be interpreted to indicate an organization of activity within infected cells which influences the

parasite profoundly. With the presence and promise of methods applicable to explorations of the now largely recondite structure and function of cells in their molecular aspects, and those of parasites of varying complexity, there is justifiable hope that the cell-parasite relationship will constitute a fertile field for the cytologist of the future equipped for such an adventure.

For several years in my laboratory we were concerned with evidence that parasites including virus particles actually do enter the protoplasm of cells and multiply there, because during earlier investigations of virus infections at least it was largely a matter of conjecture whether or not virus multiplied outside, on the surface of or only in the interior of the cells affected. The specific intracellular inclusions of certain virus diseases were thought by some observers to be mere products of degeneration. The problem was a difficult one because virus particles as such are not identifiable with certainty in the intact cell. In the case of protozoal, bacterial and rickettsial infections one could proceed with more confidence, because these parasites could be seen and identified by their morphological features.

To explore the relationship of virus to infected cells Dr. Eugene Woodruff and I concentrated on the disease fowl-pox, and succeeded in demonstrating that virus is not only present in the infected cell but constitutes a large component of the specific cellular inclusion, the Bollinger body.<sup>2</sup>

In fowl-pox the virus affects particularly epithelial cells of unfeathered parts of chicken skin. The initial lesion might be located in epithelium of the oral mucosa or in the crop. From such a focus virus enters the blood stream and localizes secondarily in unfeathered skin areas, such as the comb, wattles, eyelids and follicles if the feathers be plucked. The epithelial cells multiply by mitosis and individually enlarge to form a wart-like nodule or pock. The infection starts in the basal layer of epithelial cells and eventually it seems that every cell in the lesion gives evidence of involvement. Specifically each cell comes to contain a large round, oval or slightly lobulated refractive body or mass situated in the cytoplasm. The volume of the cell is increased apparently by an excess of water, and in fixed preparations the cytoplasm is pale and delicately reticulated.

When the infected tissue is fragmented and placed in an alkaline solution of trypsin the cells disintegrate and the compact inclusions are liberated. The latter are so substantial and of such consistency that they were easily manipulated. After repeated washings no virus was demonstrated in the fluid bathing them, yet when they were picked up individually in a capillary pipette and inserted into a follicle from which the feather had been plucked, that follicle developed the typical lesion of fowl-pox. Likewise a follicle could be infected by inserting into it a fragment of a single inclusion. Thus it was demonstrated that the specific intracellular inclusion of fowl-pox is individually and fractionally infective. Each specific inclusion or Bollinger body is composed of thousands of coccoid structures of uniform size just visible with the light microscope. These particles, the so-called elementary

bodies, are embedded in a lipoprotein matrix that gives form and consistency to the inclusion. The elementary bodies are now considered to represent virus units.

These experiments I believe offer the clearest demonstration of the presence of virus within infected cells and in association with a specific inclusion, although there is much other evidence of various sorts that strengthens the view that all known viruses enter cells and multiply only in a protoplasmic medium. It is less difficult to assure oneself that certain protozoa, bacteria and rickettsia invade cells and multiply in them, because these parasites are larger, more characteristic in their morphology and can be colored by suitable dyes which disclose distinctive characters. Consequently the now generally accepted view that many kinds of parasites penetrate and multiply exclusively in living cells of the host has a very substantial justification from observation and experiment.

Accepting the evidence then that in many specific infections individual parasites or infective agents in some fashion, usually obscure, find their way to the surface of specific living cells, penetrate them through the interplay of surface tensions, and multiply in the protoplasmic medium, the pathologist is confronted with the ultimate problem of cytology toward which much biological investigation is now converging, namely, the structure and function of the living cell—in this case the structure and function of the living cell as a culture medium for parasites.

Infectious agents are delicate indicators of differences in protoplasmic media and inasmuch as they can gain admittance, the one or another of them, to the interior environment of probably every type of cell in animal and plant bodies, I suspect that they will prove to be most useful tools with which to explore experimentally intracellular organization and activities. It is my chief purpose to point out just a few significant though gross indications that infectious agents are extremely sensitive to conditions in the protoplasmic environment. It appears from these indications that protoplasm may not be homogeneous in structure or uniform in activity with respect to its adaptability to requirements of the parasite but may be possessed of an organization that is reflected by the behavior of the invading agent, and further that the parasitic agent can alter profoundly and in different ways the intracellular medium which it at first utilizes for its own reproduction.

Not only are obligate intracellular parasites naturally host-adapted but it is well known that they are highly specific with respect to their ability to induce lesions in the different types of cell of a susceptible host. Sometimes with a particular virus this cell specificity is amazing. One of the most striking examples in our experience is the behavior of the virus of canine oral warts. This is not an uncommon disease of dogs and manifests itself by papillomatous growths upon the oral mucosa especially of the lips. These growths sometimes attain a considerable size that is, a few centimeters in diameter. The virus is easily filterable, and upon inoculation by injection

into or scarification of the oral mucosa it reveals its effects after about 30 days by the presence of epithelial plaques which grow rapidly. All of our efforts to infect other epithelia of the dog, including that of perioral skin, conjunctiva, prepuce and vagina, entirely failed.<sup>3</sup> This lack of ability of the virus to affect other than oral epithelium might be due to an inability to penetrate other cells or to failure of their protoplasm to provide suitable conditions for its multiplication. It would seem that the latter were more likely, for some viruses at least can become modified by continued passage in unusual environments so that they multiply abundantly in cells to which the original strain was unaccustomed. We have observed this both with strains of vaccinia and herpes simplex viruses.

It is of especial interest to observe that after an obligate intracellular parasite enters the cytoplasm of a cell able to support its growth, conditions existing therein determine whether or not it will be best accommodated by one of the two chief structural components namely, the cytoplasm or the nucleus. It is not known whether every infectious agent of this kind that gains access to the cytoplasm likewise penetrates the nucleus, but if so only certain ones find in that organ advantageous conditions for multiplication. It is possible that some infectious agents can only be reproduced within nucleoplasm and simply pass through the cytoplasm without being affected by it. In any case those that are known to multiply in the nucleus appear to penetrate its surface in much the same manner as they do the cytoplasmic surfaces. The intranuclear environment has long been known to afford conditions for parasitic growth in some of the lower forms of life, such as the paramecia. Among the infective diseases of the protozoa, one that has received careful study is that induced by several representatives of a particular genus of microorganisms discovered, according to Metchnikoff, by Johannes Muller in 1856 and investigated by Hafkine.<sup>4</sup> Hafkine found that paramecia are occasionally infected by needle-shaped or spirillar parasites which penetrate, sometimes into the macronucleus, sometimes into the micronucleus, reproducing prolifically only in these structures and giving rise to a marked hypertrophy of them. In spite of this invasion the paramecium may continue to exist and carry on its reproductive processes.

Among infections of higher animals many examples could be cited where evidence indicates a similar penetration of parasites into the nucleus and proliferation there. Wolbach<sup>5</sup> observed rickettsia of Rocky Mountain Spotted Fever in nuclei of certain epithelial cells of ticks, and Pinkerton and Hass<sup>6</sup> reproduced a similar picture by means of tissue cultures infected with this microorganism. Virus infections afford many instances of nuclear involvement characterized by the presence of specific inclusions which presumably indicate the local presence of the infectious agent. Among these diseases are herpes simplex, zoster and chicken-pox. There is little corresponding evidence that virus multiplies in both cytoplasm and nucleus, excepting the coincidence of inclusions in nucleus and cytoplasm in cells from

canine distemper and the salivary gland disease.<sup>7, 8</sup> That special favorable conditions exist for virus multiplication either within the nucleus or in the cytoplasm, possibly exclusively in particular instances, is indicated by the fact that a single cell can be infected by two viruses simultaneously, the one, for example herpes simplex, inducing characteristic changes in the nucleus, the other, be it fowl-pox, vaccinia or rabies, bringing about its specific inclusion in the cytoplasm.<sup>9</sup>

Not only may parasites find their most fertile soil in either nucleus or cytoplasm but of particular interest is the topographical relationship of certain of these agents to the latter medium in which they orient themselves in such a way as to indicate a structural and functional organization that offers some parasites a preferential environment for multiplication. I should like therefore to direct your attention to several instances of specific infections in which the intracytoplasmic parasite characteristically occupies a particular locus in the cytoplasm. Examples may be drawn from protozoal, bacterial, rickettsial and viral infections and they will be considered in this order.

One of the most striking examples of "selective" localization of a protozoan parasite in the cytoplasm of infected cells was described by Tyzzer<sup>10</sup> in his study of coccidiosis in gallinaceous birds. So constant were the positions assumed by different species of coccidia within the same type of epithelial cells of the intestine of chickens that their respective locations were most helpful in distinguishing them. Following is Tyzzer's description:

By a comparative review of the relation established by parasite and host-cell, various depths of penetration and a variety of reactions became apparent. In *Cryptosporidium* we have a coccidium which penetrates the cuticular layer but never enters the cytoplasm of the epithelial cell. As it increases in size it bulges out from the surface of the epithelium but nevertheless remains fixed to the cuticular layer. *Eimeria acervulina* penetrates the cytoplasm but the small growing forms are very superficially situated. The schizonts require more space but lie just beneath the surface. . . . *Eimeria mitis* penetrates deeply so that it commonly starts its development in the region of the cell's nucleus, and often below it. . . . Such distinctive host-cell-reactions are of considerable assistance in the differentiation of species.

Similar though less striking instances of intracellular localization can be found in certain bacterial infections. Recent studies of Buddingh and Womack<sup>11</sup> have shown that the developing chick embryo can be readily infected by the *Brucella* group of microorganisms. These bacteria show an especial predilection for vascular endothelium. They penetrate these cells and proliferate abundantly in their cytoplasm. They can likewise penetrate and grow within the cytoplasm of certain epithelial cells including those of the hepatic parenchyma. It is in the liver indeed that a rather striking contrast can be observed between the pattern of growth within the Kupffer cells and that within parenchymal epithelium. The difference is sufficiently distinct to permit one easily to distinguish the two types of infected cells although each is filled with parasites. In the infected liver cell the micro-

organisms appear to be uniformly distributed throughout the cytoplasm increasing its bulk considerably. In the cytoplasm of a Kupffer cell they are distinctly compartmentalized as if there were numerous colonies separated by cytoplasmic partitions. This disposition of the multiplying parasites might be attributed to a segregating effect of cytoplasmic activity or to a possible compression of protoplasmic fibers or to a gelation of the medium resulting from bacterial products. No such segregation is to be observed in infected hepatic cells or in those of the chorionic epithelium. In other similar experiments with *Pasteurella tularensis*, infected epithelium of chorion and liver showed no evidence of compartmentalization.

In leprosy we have an example of an infectious disease in which a bacillary parasite penetrates certain cells of the host and multiplies apparently exclusively in the cytoplasmic medium. Although some types of epithelium may be penetrated and can afford suitable conditions for growth, it is the large mononuclear mesodermal "lepra cell" that is characteristically involved and accounts for the peculiar histologic features of leprosy. The intracytoplasmic environment of these cells is the preferential and presumably the essential soil for the maintenance of the parasite and consequently of the disease.

It is characteristic of the "lepra cell" that there are multiple foci or colonies of Hansen's bacillus in single cells including the giant cells that frequently form in a lesion. These compact and compartmentalized colonies, separated by cytoplasmic partitions, form the characteristic "globi," familiar to the student of leprosy. There is some indication that they form about the surfaces of droplets of fat which accumulate in the "lepra cell," reminiscent of the capsule of elementary bodies of fowl-pox in early stages of infection of epithelial cells in which lipid droplets appear as the first microscopic evidence of infection.

Although the parasite of leprosy enters and grows on occasions within epithelium of the skin and sweat glands, compartmentalization and the formation of multiple "globi" do not occur in these cells.

Although obligate intracellular parasitism of the bacillus of leprosy can be reasonably assumed, there is better evidence that rickettsia multiply only in living cells. In his studies of the lesions of Rocky Mountain spotted fever in mammals and in the tick, Wolbach first described the localization of the rickettsia within cells of the former generally in the cytoplasm of endothelium and in smooth muscles of arterioles; but in infected ticks, they were also situated within nuclei of the epithelial cells of the Malpighian tubules, rectal sac, intestine and salivary glands. Intracellular localization of these parasites was especially studied by Pinkerton and Hass by means of tissue cultures of membranous exudate from the scrotal sac of infected guinea pigs. These authors described the outstanding feature of the picture to be the predilection of the rickettsia for the nuclei of cells. In several preparations, the majority of infected cells showed only nuclear involvement. The

majority of cells in which the cytoplasm was infected contained less than 50 microorganisms, and in no instance did the entire cytoplasmic volume become occupied by closely packed microorganisms. This was in striking contrast with similar cells infected by the rickettsia of louse borne typhus. In typhus infection the nucleus of involved cells never contained parasites but the cytoplasm became distended with great masses of them. It is of interest that infection of the nucleus with Rocky Mountain spotted fever parasites was characterized by a clustering of the microorganisms into more or less compact masses distributed through the nucleoplasm. The reason for the clustering of parasites in nuclei and their diffuse distribution in cytoplasm was not apparent. One may judge from these experiments that the cytoplasm of the scrotal cells is not a good medium for growth of the parasites and that not infrequently a microorganism enters it only to traverse its substance, reach the nucleus, penetrate it and multiply therein abundantly. In contrast these investigators found that typhus rickettsia occasionally form separate groups in the cytoplasm of the cells in which they grow. The partitions between the groups are often indefinite because the cytoplasm becomes filled to the point of bursting.

Recently I had the opportunity to study epithelial cells of the mucosa of the yolk sac of chick embryos which were infected as a result of injecting pure cultures of a variety of pathogenic microorganisms into the yolk. Included in the group studied were yolk sacs infected with louse-borne, and others infected with flea-borne rickettsias of typhus fever. The contrasting intracellular localization of the parasites was striking. In neither infection were nuclei penetrated as in Rocky Mountain spotted fever, but heavy intracytoplasmic growth occurred. In the case of *R. prowazeki* epithelial cells became filled and distended by parasites which in different cells presented two morphological appearances. In the great majority the cytoplasm became filled with minute coccoid or short bacillary forms. More rarely other cells contained exclusively long filamentous forms apparently interwoven in a loose fashion. These two forms of this parasite have been noted by Wolbach and by Pinkerton and Hass, but no satisfactory explanation of the difference is at hand.

Epithelium of the yolk sac infected with *R. mooseri* presented a quite different and a significant picture. In each infected cell the growing mass of flea-borne rickettsia was located only in the basal pole between the nucleus and the basement membrane. There was no distention of cells and no apparent involvement of the cytoplasm distal to the nucleus. It seems quite clear from these preparations that epithelial cells of the chick yolk-sac afford for this rickettsia localized, favorable conditions within the cytoplasm restricted to the basal pole and most favorable adjacent to the nucleus. So far as I know such an intracellular disposition of this parasite has not hitherto been described.

Among virus infections only those that afford evidence of location and growth within cells, such as by the formation of inclusions which can be

interpreted to be partly composed of elementary virus particles, permit one to speculate upon possible intracellular organization that might provide specially favorable or unfavorable environments for their multiplication. It can be reasonably conjectured from numerous examples that some viruses enter and multiply within the nucleus, perhaps exclusively, while others remain confined to the cytoplasm. There is no clear indication at present that different parts of the nucleus provide more or less favorable conditions for virus growth although it appears that nuclear activity and structure may be affected differently by different infectious agents that presumably multiply within it.

A variety of morphological appearances in the cytoplasm of infected epithelial cells can be illustrated by examples from the pox group of virus lesions. These infections have the advantage too that their etiological agents are quite comparable with each other and are large enough to be identified in suitably stained preparations, so that their participation in the composition of the respective cytoplasmic inclusions is no longer reasonably in doubt.

In fowl-pox the first indication of infection of an epithelial cell is the occurrence of one or more small globules of fat apparently indiscriminately distributed within the cytoplasm. They enlarge and one can then demonstrate about them an encapsulation of acidophilic material. This material increases proportionately as the inclusion enlarges. The bodies scattered through the cytoplasm move about in such a way as to join each other eventually to form by fusion a single large spherical, oval or irregularly elliptical mass which constitutes the "mature" Bollinger body. This consists of thousands of elementary bodies embedded in a lipo-protein matrix. There is no indication that one area of the cytoplasm is more adaptable to their formation than another. Nucleoli may become enlarged and nucleolar particles may be extruded into the cytoplasm.

Infection of human cutaneous epithelium with virus of molluscum contagiosum likewise manifests itself by cytoplasmic changes but of a different kind.<sup>12</sup> In early stages of infection conspicuous nucleolar disturbances are observed although the virus is confined to the cytoplasm. The nucleoli enlarge and conspicuous particles of nucleolar material, often surrounded by a sort of misty halo, appear in the cytoplasm. Early evidences of cytoplasmic involvement are observed in the central portion of the cytoplasm. Here there seems to be a sort of condensation about which a series of clear vacuoles are seen in fixed preparations. These vacuolated areas probably contained a clear fluid in which no fat is stainable. About the periphery of the vacuoles dense confluent zones appear in the cytoplasm and in this denser material lie the elementary molluscum bodies, indistinguishable in stained smear preparations from those of fowl-pox, small-pox and vaccinia. The dense and basophilic material increases in amount until it finally quite fills the cell and distends it, the nucleus being forced to the periphery. At this final stage no vacuoles are to be seen, but the architecture of the cytoplasm with its abundance of newly formed elements is quite characteristic in that it is definitely



compartmentalized by thin partitions which outline the separate areas filled with elementary bodies. The elementary bodies are held together by a sticky substrate which prevents manipulation of the gross inclusion after digesting the cytoplasmic surfaces and partitions by means of trypsin. In the development of infection with the virus of mollusum contagiosum then, there does not appear to be an indiscriminate localization in the cytoplasm but rather a preferential one in the center of its mass.

With the viruses of small-pox and vaccinia the case is different for both of them develop their respective cytoplasmic inclusions (Guarnieri bodies) in close relation to the nucleus of the infected cell. The surface of the nucleus on one or two sides is frequently indented by the inclusions. In the case of vaccinia, especially in infections of the chick embryo, large pyramidal inclusions are seen with their bases closely adjacent to the nucleus. One can infer from such appearances that a perinuclear environment is especially adaptable to multiplication of these immunologically closely related parasites.

These examples of intracellular parasitism should be sufficient to illustrate the variable interactions and relationships that transpire during the adaptations of the substances and energies of the parasite on the one hand and those of the host-cell on the other. They likewise indicate the presence of peculiar conditions in the cell supporting multiplication of a parasite which predispose to a localization and proliferation of the infectious agent either in the nucleus, or in the cytoplasm, rarely in both. Furthermore morphological changes are presented that can be adduced as evidence of the existence of a structural and functional organization of the cytoplasmic medium that affords a topographically preferential orientation to the multiplication of a particular parasite. In one instance it might be the immediate perinuclear environment as in vaccinia and endemic typhus, in another the base of the cell or its antipode as in coccidiosis and again it might be a more central location as illustrated by mollusum contagiosum. The occurrence of such dispositions of parasitic multiplication within the cytoplasm can be assumed to indicate especial activities or concentration of activities at such places that predispose or perhaps exclusively provide suitable environments for the consummation of infection.

It is encouraging to note that already methods are being developed and used successfully for exploring localized activities within the living cell. These methods, chemical and physical, may be exemplified by the histochemical studies of Dustin<sup>13</sup> whose results suggest that the vital staining, by such basic dyes as neutral red, of cytoplasmic vacuoles belonging to the Golgi zone or those newly formed, may be the consequence of the existence of small quantities of ribonucleoproteins within these vacuoles; or, by the illuminating qualitative and quantitative microspectrometric studies of Caspersson and his colleagues which relate the nucleus and nucleolus to the cytoplasmic protein-forming system of the cell.<sup>14</sup> Other newer micro methods applicable to studies of intracellular localization include use of the electron microscope

and the radioautographic technic. By the application of these and other technics to be devised we shall sooner or later begin to learn something about the nature of the internal cellular environment and its differentiation with respect to support of parasitic infection. Conversely parasitic infections of cells might be useful tools in such cytological explorations.

During the past century and with accelerating speed, analyses of biological materials have placed in the hands of scientists a number of identified and purified agents that influence profoundly physiological activity in one way or another. Enzymes, hormones, and vitamins are examples. In analytical research the parasitologist, in a broad sense, has identified pathogenic agents in great abundance and variety. He has learned to isolate them and cultivate them in pure strain. If he has not succeeded in enabling them in some instances to reproduce themselves on dead media, he has endeavored and often succeeded in purifying them in quantity by physical and sometimes by chemical means. In the case of those that multiply only in living cells he has often provided suitable living media in the form of new and unaccustomed hosts available for laboratory investigation. But, as with the biochemist, the pharmacologist and physiologist, he has not yet been able to delve deeply into the other element of the equation of biological activity namely, the living cell with which the agents react. It is one thing to know an inciting agent of a set of biological processes, quite another and a much more complex one to understand the medium with which the agent must interact. Cytology indeed has progressed, but it lags far behind the analysis of activators.

After reviewing progress of cytology during the past three quarter-centuries Schrader<sup>15</sup> has recently summed up the situation as follows: "It is taking no great risk to predict that 1950 will mark the end of a period, just as sharply as did 1925 and 1900 (in the progress of cytology). Whether he is pleased or not, the cytologist of the next quarter-century will find his co-workers in the laboratories of the biochemist and biophysicist. . . . Moreover, it is already obvious that in this newer alliance the cytologist will not play the subsidiary rôle that he has had in the recent past, for it is on the foundations constructed by him that this building of the future will arise." In similar vein it may be said with equal appropriateness that in the future the co-workers of the parasitologist will be found in the laboratories of the biochemist, the biophysicist, the cytologist and the pathologist, all bringing their energies and tools to bear upon that enigmatic and ultimate biologically active system—the cell. In this broadly coöperative research the agents provided by the parasitologist, the protozoa, bacteria, rickettsia, and viruses, which can be introduced into appropriate cells to loose there a series of reactions, should prove of great usefulness in attempts to discover the structure and capacities of cells. Any knowledge thus gained would have additional value for the pathologist who is seeking to understand the chain of events underlying infection and the full explanation of therapeutic benefits to be derived from chemical and immunological interventions.

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## THE NEWER ANALGESIC DRUGS; THEIR USE AND ABUSE\*

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ALTHOUGH morphine has been regarded for over a hundred years as the most effective and reliable compound for the relief of the more severe grades of pain, the drug has many undesirable properties. It produces respiratory depression; it increases the activity and tone of the smooth muscle of the gastrointestinal, biliary, and urinary tracts, causing constipation, spasm of the gall-bladder and bile ducts, and urinary retention; it frequently causes nausea and vomiting; and it may induce itching of the skin. If morphine has to be administered over a long period of time, tolerance to the analgesic effect develops so that the dose must be increased from time to time to obtain adequate pain relief. Under such conditions of prolonged use, physical dependence on the drug develops. The euphoria induced by morphine, although likely a desirable action which may be necessary for pain relief, leads to the abuse of the drug by persons with susceptible personalities, resulting in addiction.

Because of these undesirable actions, a constant search has been carried on for drugs which would be equal to morphine in analgesic action but which would have fewer side effects, and particularly for drugs which would have less addiction liability. Little progress was made until 1939 when Small, Eddy, Mosettig, and Himmelsbach<sup>1</sup> issued a summary of their studies on methyldihydromorphinone, or metopon, a new member of the morphine series of drugs which appeared to possess some distinct advantages over morphine. Since 1939, two new potent analgesic drugs, which are not chemically related to morphine or to each other, have been discovered. These are meperidine, or demerol (ethyl 1-methyl-4-phenylpiperidine-4-carboxylate), and methadon, or amidone (6-dimethylamino-4-4-diphenyl-3-heptanone). The discovery of both these drugs must be credited to the German chemists and pharmacologists of the I. G. Farbenindustrie.<sup>2</sup> The chemical dissimilarity of metopon, methadon, and meperidine is shown in figure 1. The fact that, despite the lack of chemical resemblance, meperidine and metopon have much in common pharmacologically with each other and with morphine is rather astonishing and has given great impetus to the search for more effective analgesics. We can expect the development of new compounds in the meperidine and methadon series which may possess advantages over the original drugs; and other analgesic drugs with molecular structures differing from any yet known may be discovered. While this quest for new

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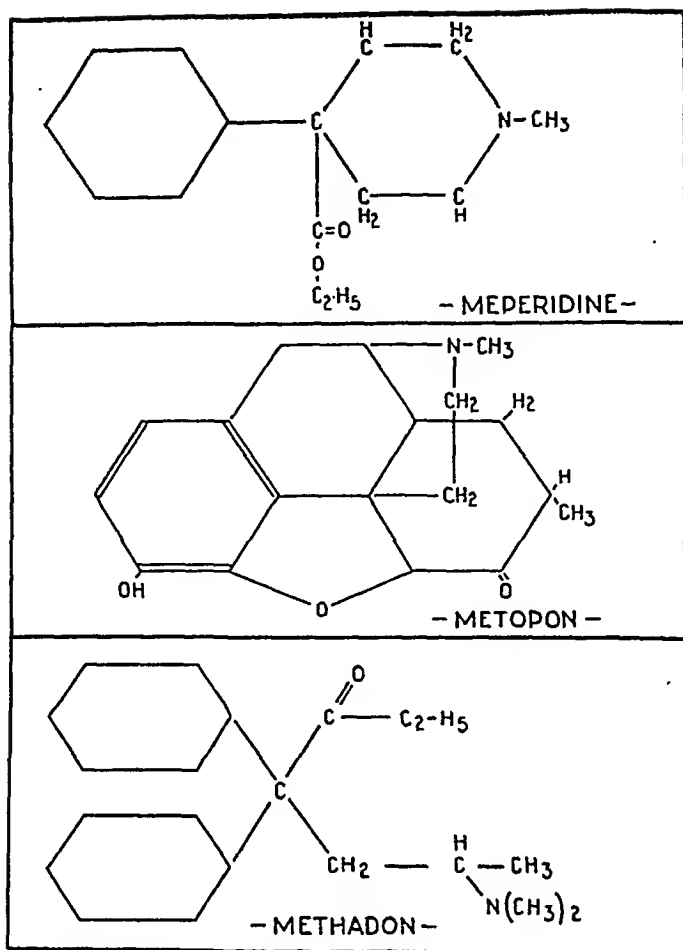


FIG. 1. Structural formulae of the new analgesics.

substances with pain-relieving actions is desirable, it will also bring confusion. The choice of an analgesic drug may soon be as complex as the choice of an hypnotic drug. It therefore seems wise at this point to attempt to assess the advantages of the three new analgesics, metopon, meperidine, and methadon, to consider their addiction liability, and to describe or discuss some indications for their use.

### ANALGESIC EFFECT

Since the presence of severe pain which cannot be relieved by simpler means is the major indication for the administration of any of the potent analgesic drugs, an understanding of the mechanism of relief of pain by these drugs is important in their use. Wolff and his collaborators<sup>8</sup> have developed a theory of analgesia which states that the pain-relieving effects of the opiates, or similar drugs, are due to a combination of three factors: (1) elevation of the threshold for perception of pain, (2) an alteration of the emotional reaction to pain, and (3) the production of sedation and sleep. Elevation of the pain threshold and the production of sedation and sleep

appear to be less important than alteration of the emotional reaction to pain. If morphine is given after the experimental production of pain in human subjects, the pain threshold is not elevated and yet the pain is relieved.<sup>3</sup> Since most patients who receive morphine have experienced pain prior to administration of the drug, elevation of the pain threshold is probably of minor importance in clinical practice. Relief of pain is not necessarily associated with the production of sedation and sleep. The barbiturates, though powerful sedative and hypnotic drugs, are not effective analgesics. Most of the pain-relieving action of the powerful analgesics must, therefore, be ascribed to a rather specific alteration in the emotional reaction to pain. A person with severe pain who receives a dose of morphine, or some other potent analgesic drug, may continue to perceive the pain, but, since the pain seems to have lost its dangerous quality, the patient disregards it and, under the hypnotic influence of the drug, drifts off to sleep. It seems reasonable to assume that the alteration of the emotional reaction to pain by the analgesic drugs may be associated with the euphoria produced by these compounds. The exact sites and mechanism of action of these drugs within the central nervous system are not yet understood, but the fact that patients who have had prefrontal lobotomy for the relief of pain continue to perceive pain but are not disturbed by it, suggests that the important effect of altering the reaction to pain may be mediated through an action on the cortex of the frontal lobe.

TABLE I  
Comparative Efficacy of Single Doses of New Drugs in Altering  
Various Factors Concerned in Analgesia

Drug	Dose Mg.	Elevation of Pain Threshold	Alteration of Reaction to Pain	Sedation	Duration of Clinical Relief of Pain-Hours
Morphine	10	2	2	1	4 Hours
Metopon	6	1	1	3	4 Hours
Meperidine	100	4	3	2	3 Hours
Methadon	5-10	3	4	4	4-10 Hours

The figure 1 indicates the most effective of the four drugs in producing the effect noted; the figure 4 indicates the least effective of the four drugs.

The comparative efficacy of the three new analgesics and of morphine in altering the factors concerned in analgesia is shown in table 1. With the exception of the elevation of the pain threshold, which has been measured, the comparisons represent the personal opinions of the author, and were assigned on the basis of experience with all the drugs. The table shows that morphine and metopon are the two most effective drugs and that meperidine and methadon are less effective. However, if the drugs are used every four to six hours, the order is radically altered. Methadon is a slowly acting,

cumulative drug and, when repeatedly administered, exerts an effect on the reaction to pain equal to that produced by morphine and excels morphine in sedative and hypnotic effect. Methadon is, therefore, not a good drug for pre-anesthetic medication and is only fairly effective in situations requiring very rapid relief of pain, but it is a very good drug for the relief of chronic pain. Under conditions of repeated dosage, methadon is equal to morphine and metopon in inducing analgesia. Meperidine, though fairly effective, is not as reliable or as potent an analgesic as are the other three drugs.

### OTHER PHARMACOLOGICAL ACTIONS

*Metopon.* In minimal analgesic doses, metopon is less likely to produce sedation and mental dullness than is morphine.<sup>4, 5, 6</sup> While respiratory depression is less marked after the administration of metopon than after the administration of morphine,<sup>1</sup> metopon, in conjunction with inhalation anesthetics, may produce serious respiratory depression<sup>5</sup> and is, therefore, contraindicated as pre-anesthetic medication. Metopon is almost as effective in relieving pain when given by mouth as when administered hypodermically.<sup>1, 4, 5</sup> Due to difficulties in manufacture, metopon is about 10 times as expensive as morphine, and the amount available for use may always be limited.<sup>4</sup>

*Meperidine.* Meperidine is said to produce serious respiratory depression less often than does morphine.<sup>7, 8, 9</sup> This statement seems to be based on clinical impressions or on counts of respiratory rate and not on actual measurements of respiratory minute volume. Nausea and vomiting are also claimed to occur less frequently than after morphine. If, however, one compares the figures published by Batterman<sup>7</sup> on the incidence of nausea and vomiting after meperidine with those of Lee<sup>5</sup> on the incidence of nausea and vomiting after morphine, it would appear that nausea and vomiting occur more often after meperidine than after morphine. Batterman gives the incidence of nausea after parenteral administration of meperidine to hospitalized patients as 8.4 per cent and the incidence of vomiting as 3.8 per cent; Lee found that the incidence of nausea after the subcutaneous administration of morphine was 3.5 per cent and the incidence of vomiting was 2.3 per cent. Despite these figures, it is common clinical experience that persons who cannot tolerate morphine because of nausea may tolerate meperidine. In man, meperidine relaxes spasm of the smooth muscle of the gastrointestinal tract<sup>7, 10</sup> and the ureter.<sup>11</sup> Although the rôle of the spasmolytic action of meperidine in relieving colicky pain has been over-emphasized, the drug at least does not increase spasm of smooth muscle as does morphine. Meperidine does not produce constipation. It is effective when administered by mouth, but is more expensive than morphine.

*Methadon.* Methadon is very similar to morphine in all its pharmacologic actions.<sup>12, 13, 14, 15, 16, 17</sup> It depresses respiration as much as does morphine,<sup>16</sup> causes nausea and vomiting just as frequently,<sup>16</sup> and is constipating

It is quite irritating when injected subcutaneously, and, if injected repeatedly into the same sites, causes severe inflammation and induration of the skin.<sup>18</sup> Nausea and vomiting occur so frequently after oral administration that the drug cannot be used by this route.<sup>16</sup>

### ADDICTION LIABILITY

The danger of addiction is one of the most important matters which must be considered in evaluating the proper use of a new drug. Drug addiction can be defined as the abuse of a drug to such an extent that the individual has lost the power of self control with reference to use of drug, and to such an extent that the individual or society is harmed. Himmelsbach and Small<sup>19</sup> have described addiction to the opiate drugs as consisting of three closely intertwined factors: tolerance, physical dependence, and habituation or psychic or emotional dependence. Tolerance may be defined as a diminishing effect on repetition of the same dose of a drug. Physical dependence refers to an altered bodily state brought about by repeated administration of a drug which necessitates continued use of the drug to maintain physiological normality. Physical dependence is manifest by the appearance of a characteristic illness when the drug is withheld. Habituation means psychic or emotional dependence on a drug—the substitution of the use of the drug for all other aims and objects in life. The extent to which these various factors are involved in addiction varies with the person and with the drug. Physical dependence has, in the past, been regarded as the most important quality of an addicting drug. Emotional dependence, however, is now believed to be the most important characteristic. It is the quality responsible for the initiation of addiction. A person becomes addicted, not because he needs the drug to prevent the appearance of a withdrawal illness, but because he enjoyed the subjective sensations the drug produces. Addicts who have been withdrawn from drugs repeatedly relapse to the use of the drug because they desire the pleasant effects of the drug and the relief of psychic or emotional stress which it brings, and not because they need the drug to relieve symptoms of a withdrawal illness. In assessing addiction liability one should, therefore, give the greatest weight to the habituation liability of the drug in question.

### TOLERANCE

Tolerance develops to many actions of metopon,<sup>5</sup> methadon,<sup>18</sup> and meperidine,<sup>7, 20</sup> including the sedative and emetic effects, and the pain threshold-elevating action (figure 2). Partial tolerance to the respiratory and circulatory effects probably occurs. Tolerance to the clinical analgesic effects of all three drugs develops more slowly than does tolerance to the analgesic effect of morphine.<sup>4, 5, 6, 7, 18</sup> The slow development of tolerance is the greatest advantage these drugs possess over morphine. Metopon has one further advantage: tolerance to the clinical analgesic effect of metopon is abolished



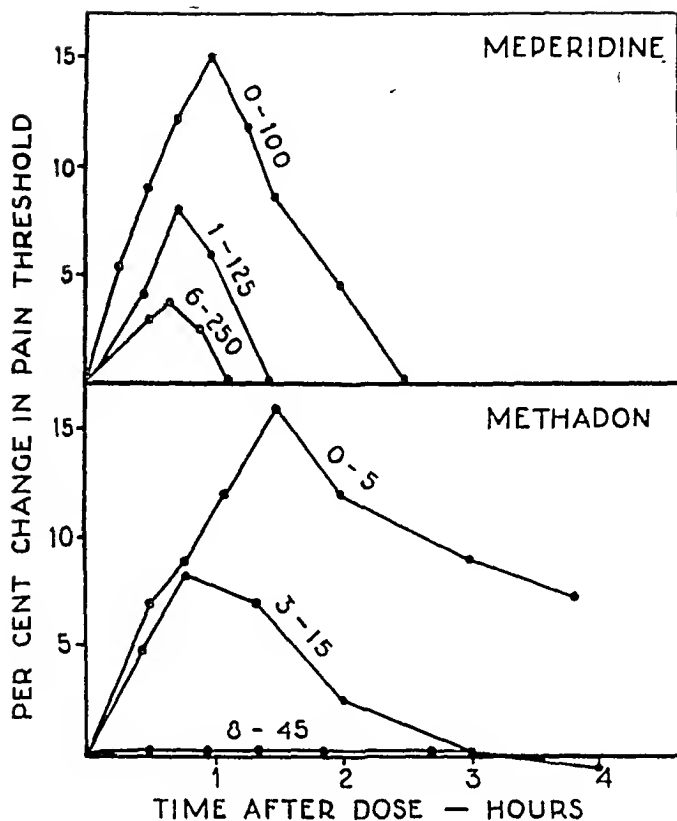


FIG. 2. Development of tolerance to pain threshold-elevating action of meperidine and methadon during addiction to either drug. Ordinates: per cent change in pain threshold calculated from the pre-dose thresholds. Abscissae: time after dose in hours. The first figure above each curve represents the week of addiction in which the curve was obtained. The second figure above each curve represents the dose of the drug being administered at that time. Note the decline in the response as addiction proceeds.

by withdrawing the drug for only eight to 14 hours.<sup>5</sup> This rapid loss of tolerance has not been shown to occur with any other analgesic drug.

### PHYSICAL DEPENDENCE

Metopon, meperidine, and methadon all have physical dependence liability. When metopon<sup>21</sup> or meperidine<sup>22</sup> was substituted for morphine, signs of the abstinence syndrome were partially, but not completely, suppressed. Following withdrawal of metopon or meperidine after substitution for morphine, abstinence syndromes which were qualitatively similar to abstinence from morphine appeared very quickly.<sup>21, 22, 23</sup> Symptoms of abstinence also developed following withdrawal of meperidine after administration of large doses to former morphine addicts for 10 to 11 weeks,<sup>22</sup> or after withdrawal of metopon after 21 days or more of administration to patients for the relief of chronic painful disease.<sup>5</sup> Abstinence symptoms following withdrawal from both meperidine and metopon came on more rapidly, were less intense, and subsided more rapidly than did abstinence symptoms following withdrawal from morphine<sup>5, 21, 22</sup> (figure 3). Methadon completely relieved and

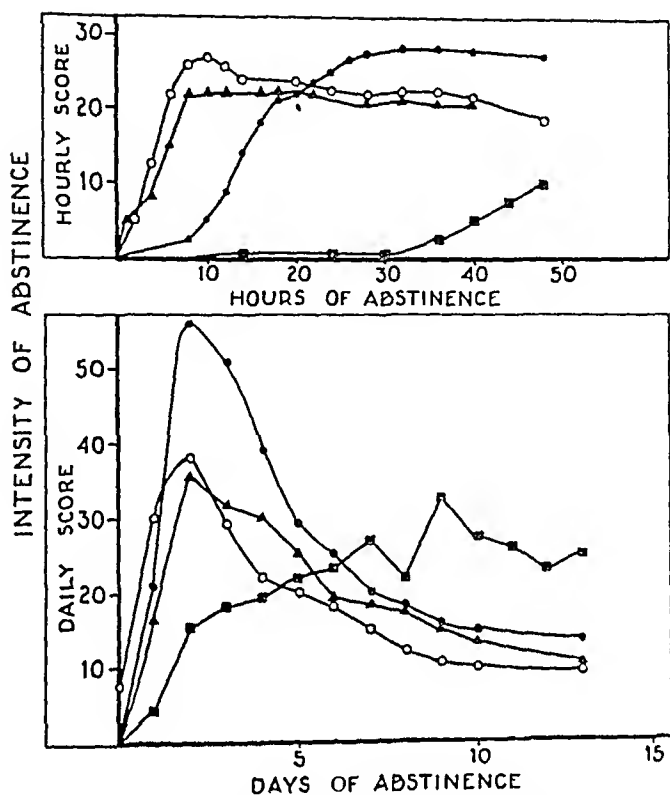


FIG. 3. Comparison of onset and intensity of abstinence after withdrawal of new analgesics. Upper curve: onset of abstinence. Ordinates: intensity of abstinence in hourly points. Abscissae: time since last dose of drug in hours. Lower curve: course of abstinence. Ordinates: intensity of abstinence in daily points. Abscissae: time since last dose in days. Solid circles: abstinence from morphine. Open circles: abstinence from methadon. Triangles: abstinence from meperidine. Squares: abstinence from metopon. Both hourly and daily point scores are calculated according to the Himmelsbach<sup>21</sup> scoring system in which arbitrary numerical values are assigned to the various signs of abstinence.

suppressed signs of abstinence from morphine.<sup>18</sup> Following withdrawal of methadon after substitution for morphine, or after administration to former morphine addicts for two to six months, an abstinence syndrome developed which came on more slowly, was much less intense, and subsided more slowly than did the abstinence syndrome following withdrawal of morphine<sup>18</sup> (figure 3). The abstinence syndrome following withdrawal of methadon was milder than the abstinence syndrome following withdrawal of metopon or meperidine. Following withdrawal of methadon, very few of the autonomic signs so characteristic of the abstinence syndrome following withdrawal from morphine, metopon, or meperidine were observed.<sup>18</sup>

#### HABITUATION

Single minimal analgesic doses of methadon<sup>12, 18, 24</sup> and metopon<sup>4, 5</sup> seldom produce significant euphoric reaction in either non-addicts or former morphine addicts. In our experience, despite the literature on the subject,<sup>7</sup> single minimal analgesic doses of meperidine frequently cause mild euphoria. If, however, the drugs are administered in doses as large as one would expect

addicts to use, both metopon<sup>25</sup> and methadon<sup>18</sup> produce grades of euphoria which equal, or exceed, those induced by morphine, and which are more intense than the euphoria after any dose of meperidine. The euphoria after large doses of metopon is maintained as long as euphoria following morphine,<sup>25</sup> and the euphoria after large doses of methadon is sustained for 36 to 48 hours.<sup>18</sup> Euphoria after meperidine lasts only one or two hours. For this reason, meperidine is not as popular with experienced morphine addicts as are metopon and methadon. The behavior of men experimentally addicted to methadon was similar to that seen during morphine addiction.<sup>18</sup> They ceased all productive activity, neglected their personal appearances, and spent a great deal of time in bed in a semi-somnolent state. Following withdrawal of methadon, the patients complained, begged for the drug, and would take additional doses months after all signs of physical dependence had disappeared.<sup>18</sup> The behavior of patients addicted to meperidine is also similar to that of patients addicted to morphine.<sup>20</sup>

The evidence forces us to conclude that all three drugs are addicting. Any differences noted in the addiction liability of the new analgesic drugs from that of morphine are differences in degree, not kind. Tolerance has developed to actions of all three drugs. Physical dependence has been demonstrated after prolonged administration of all three drugs and, more important, all three drugs have been shown to possess considerable habituation liability.

#### "NATURAL" ADDICTION

Metopon and methadon have not been available for a sufficient length of time for non-experimental addiction to occur. For some time a controversy was carried on concerning the addiction liability of meperidine. It was claimed that cases of addiction had not occurred in persons not formerly addicted to morphine (so-called "primary" addicts). This view is no longer tenable since a number of cases of "primary" addiction to meperidine have been reported in the literature.<sup>26</sup> More than 20 persons primarily addicted to meperidine have been studied at the U. S. Public Health Service Hospital, Lexington, Ky. Their histories showed that their behavior was similar to the behavior of morphine addicts. They substituted the use of meperidine for all other aims and objects in life; they spent their savings for the drug, left their families for it, and lied and stole to obtain it. In one respect, addiction to meperidine in these cases was more undesirable than addiction to morphine. The patients used such large doses that the serious toxic effects noted by Andrews<sup>27</sup>—tremors, increased startle responses, and even epileptiform seizures—developed.

#### CLINICAL APPLICATIONS OF THE NEW ANALGESICS

It is not to be expected that these new drugs will completely replace morphine. Due to its quick but long-lasting action, its reliability, its power-

ful sedative action, and its relative cheapness, morphine is still the choice for most patients requiring relief of pain for periods of less than 14 days.

The use of metopon has been restricted by the National Research Council to persons with chronic painful diseases, and the drug is available for oral use only. This decision was taken because of the slow development of tolerance to metopon, the rapid loss of tolerance on short withdrawal, the low degree of sedation, its effectiveness by the oral route, and because of the limitation of the amount available due to difficulties in manufacturing.

Meperidine seems to have lost popularity because it is not as reliable or as long-lasting an analgesic as is morphine or methadon. Severe grades of pain are often not well controlled with meperidine. The drug, however, deserves a trial in cases of pain associated with spasm of smooth muscle. It is also indicated for persons who are nauseated by morphine. Since it is effective orally, and since tolerance develops slowly, it is quite useful in managing chronic diseases associated with mild grades of pain.

Methadon can be used in most situations where morphine is indicated. Due to its slow cumulative action, it is probably not as desirable as morphine in situations demanding very quick relief of pain. The drug is useful in chronic diseases since tolerance develops slowly and physical dependence on the compound is quite mild. If a person with a chronic disease has received morphine for a long period of time, methadon is the only drug which can be satisfactorily substituted for the morphine, since meperidine and metopon do not completely suppress signs of the abstinence syndrome following withdrawal from morphine. The fact that methadon cannot be used orally is a great disadvantage, which largely limits its use to cases under hospital supervision. Due to the low intensity of the abstinence syndrome following withdrawal of methadon after substitution for morphine in cases strongly addicted to morphine, methadon is the drug of choice for treatment of the morphine abstinence syndrome.

#### PREVENTION OF ABUSE OF THE NEW ANALGESIC DRUGS

Meperidine, metopon, and methadon have been placed under the provisions of the Harrison Narcotic Act in order to minimize abuse of the drugs and to limit the spread of addiction to them. Physicians should keep the danger of addiction to these substances in mind and should exercise the same caution in prescribing them as is followed in prescribing morphine. The drugs should never be used when other drugs or other measures will suffice. The dosage should be held to the minimum compatible with adequate pain relief, and the interval between doses should be as great as possible. The drugs should be discontinued as soon as the need for pain relief has passed. They should never be used primarily for their sedative actions. In chronic cases, they should be administered orally whenever possible. Self medication with a hypodermic should be discouraged. The drugs should never be given intravenously, since this method produces maximum euphoria and

carries a great risk of addiction. The drugs should not be administered to persons with known psychopathic or psychoneurotic personalities unless very definite indications for the use of a potent analgesic are present. The drugs should never be used for the relief of symptoms due to alcoholic excess, since alcoholics are very prone to addiction. The drugs should never be used for the treatment of asthma, since asthmatics are also very susceptible to addiction. It is significant that several of the cases of primary addiction to meperidine observed at Lexington, Ky., became addicted as a result of administration of meperidine for the relief of asthma.

### SUMMARY

The pharmacology, addiction liability and clinical use of three new analgesic drugs—metopon, meperidine, and methadon—have been discussed.

Metopon and methadon (in repeated dosage) are as effective in relieving pain as is morphine. Metopon produces fewer side reactions than morphine. Methadon causes just as many side reactions as does morphine. Meperidine prevents spasm of smooth muscle in man, and can often be used in subjects who do not tolerate morphine well, but it is less reliable than the other three drugs.

All three drugs are addicting. The same precautions should be exercised in their use as are followed in prescribing morphine.

Morphine remains the drug of choice for most conditions requiring quick relief of pain for short periods of time. Meperidine is indicated in cases of pain associated with spasm of smooth muscle, or in persons who do not tolerate morphine well. Metopon is limited to oral use in chronic painful diseases. Methadon can be used in most instances in which morphine is indicated. It is particularly useful in cases requiring pain relief for long periods of time, and for withdrawing drugs from patients addicted to the opiates.

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## STRONGYLOIDIASIS \*

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WITHIN the past few years increasing importance has been attached to the subject of tropical medicine. The truly global aspects of World War II, the return of American soldiers from far-flung corners of the earth, and the ease and frequency of intercontinental travel have all been factors leading to stimulation of interest in this subject. Although information concerning some diseases endemic in more remote portions of the world has been widely disseminated, a few, such as strongyloidiasis, have not been sufficiently emphasized. For example, McCoy<sup>1</sup> discusses precautions taken by the Army to prevent the introduction of tropical disease; Weber<sup>2</sup> reviews roentgen-ray changes seen in tropical diseases; and Saper<sup>3</sup> discusses tropical disease in veterans of World War II, all without mentioning strongyloidiasis in their discussions. Attention should be given to this parasitic disease for several reasons: (1) The causative organism shows remarkable persistence in the human host; (2) The symptoms of the disease are more severe and perhaps somewhat more characteristic than common teaching would indicate; (3) The possibility of a fatal outcome is little appreciated; (4) There is increasing awareness that the disease is encountered not infrequently in temperate climates; (5) Considerable significance can be attached to the belief held by Faust<sup>4</sup> that *S. stercoralis* is a more recent evolutionary development among human pathogens, and because of this neither the parasite nor the host tissue as yet reacts in any fixed or regular pattern.

Probably the most important aspect of the disease is the possibility of persistence of the organism for many years following primary infection through the mechanism of hyperinfection. Consequently, many symptom-free persons who have traveled in regions where the disease is endemic are potential victims of the disease.

The case presented below is of interest for several reasons. It typifies the cases which have a long, latent period following departure from the tropics with development of severe symptoms many years later in a northern climate. The usual symptomatology of a severe infection is well illustrated, as well as the possible fatal outcome of the disease. A complete autopsy is available on a case uncomplicated by any other parasitic infestation, showing the usual findings as well as hitherto undescribed pathological changes of strongyloidiasis. Finally, the case offers an opportunity for review of the

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disease with stress on the need for consideration of the diagnosis in any person who has lived in an area where the disease is endemic.

#### CASE REPORT

The patient, a 47-year-old colored male, was first admitted to the Boston City Hospital on November 20, 1945, with the chief complaint of abdominal pain. Six days prior to admission the patient had noticed the sensation of chilliness and shortly thereafter developed severe, persistent pain in the dorsum of the left foot. Four days before admission pain in the left thigh and buttock, as well as in the lower abdomen, was noted. The lower abdominal pain steadily increased in severity and radiated to the lower back. A hot, fiery sensation was present in the skin over the latter area. Marked anorexia and insomnia were present and the patient had lost 15 pounds of weight in the year preceding admission.

The patient was born in Monserrat, British West Indies, came to Boston in 1920, and lived in this area continuously, except for one brief trip to his birthplace in 1933. In September 1944 the patient had been studied at another hospital where diagnoses of strongyloidiasis and possible mediastinal cyst were made. He had been readmitted to that hospital shortly before the onset of his present illness because of severe abdominal pain, and at that time larvae of *S. stercoralis* were again found in his stool in spite of previous gentian violet therapy.

The patient was a normally developed and well-nourished male negro in considerable distress. The positive physical findings consisted of dullness over the left anterior chest and axilla, numerous small, discrete, non-tender inguinal and popliteal nodes, and moderately severe generalized abdominal tenderness.

The white blood count on admission was 5,100, differential showing two young and 36 old polymorphonuclears, 39 lymphocytes and two monocytes. No eosinophiles were seen. The hematocrit value was 34 cm. and the sedimentation rate was 12 mm. in one hour (corrected). "Living worms" were seen in the urine on admission but failed to appear in subsequent urine examinations. Large numbers of pus cells were frequently observed in the urine and occasionally red cells were seen. Stools were positive for occult blood and showed both rhabditiform and filariform larvae of *S. stercoralis*. Repeated stool cultures for bacterial pathogens were negative. The blood total protein ranged from 4.8 to 5.4 grams. Gastric analysis showed only 10 units of total acid and no free hydrochloric acid. No sickling of red cells was detected. Lumbar puncture showed normal fluid dynamics and the spinal fluid chemistry was normal. The blood Hinton and Aschheim-Zondek tests were negative.

Roentgenographic studies revealed intestinal changes interpreted as being due to diverticula of the small bowel and marked spasm of the sigmoid and descending colon. A pressure defect of the lesser curvature of the stomach with a 30 per cent gastric residue was noted on initial examination, but this finding was not confirmed on repeated studies.

Roentgen studies of the chest disclosed a mass to the left of the heart of greater density than the heart shadow and with definite notching between it and the heart. This mass was shown by lateral films to lie in the anterior mediastinum. It did not pulsate and did not compress the esophagus. A bronchogram showed no filling of the bronchioles over the mass and no filling of the left lower anterior bronchus.

Electrocardiographic studies showed a normal cardiac axis and normal sinus rhythm.  $T_1$  and  $T_3$  were low. These findings were interpreted as being due either to myocardial damage or to some extracardiac factor.

The patient continued to complain of severe persistent abdominal pain and steadily lost weight. He had intermittent bouts of diarrhea of five to seven soft or watery stools a day. He was treated with 2 grains of gentian violet three times a day for



10 days, and while under this therapy his stools became guaiac negative and temporarily free of larvae, but the diarrhea persisted. The abdominal pain shifted from the lower abdomen to the epigastrium. A few days later he developed marked tenderness over the spinous processes of the lower thoracic and first lumbar vertebrae and tenderness over the epigastrium. The blood hemoglobin decreased steadily and the blood smear showed a constant lymphocytosis. No increase in eosinophilic granulocytes was ever seen in the blood smear.

The consensus was that the patient's clinical findings were related to the mediastinal tumor rather than to the *S. stercoralis* infestation. He was transferred to the Surgical Service for chest exploration but refused operation and left the hospital on January 11, 1946.

He was readmitted to the hospital on February 2, 1946. During the brief interval following his discharge he had continued to suffer from generalized abdominal pain, pain in the lower back, headache, anorexia and general malaise. On the day preceding readmission he vomited large amounts of greenish material on several occasions. The morning of admission he had severe itching about the anus relieved by the application of alcohol. Bowel movements had been normal in frequency and the stools were of normal consistence. Physical findings were essentially the same as on previous admission, with the exception of slight clubbing of the fingers and more marked abdominal tenderness. The white count was normal but the number of neutrophils had increased with a shift to the left.

Following admission the patient complained of increasingly severe abdominal pain. He took no food and very little water. His condition rapidly became worse and he died on the fourth hospital day.

At no time during the patient's course had the serious potentialities of the *S. stercoralis* infestation been considered. His clinical picture had been explained wholly on the basis of the existence of a malignant thoracic lesion with metastases.

#### Autopsy

A routine autopsy was performed 15 hours after death. Only the relevant pathologic findings are included.

The body was that of an emaciated, adult negro man. The mesenteric lymph nodes were enlarged to 2 or 3 cm. in diameter and were firm with a homogeneous dull yellow cut surface. A well-encapsulated, pear-shaped tumor weighing 320 grams lay in the anterior mediastinum just to the left of the midline. The apex of this tumor was at the level of the sternomanubrial joint and the base rested against the diaphragm. None of the adjacent structures were infiltrated or compressed by this tumor. On section the surface was pink, meaty and divided by thick, fibrous septa into nodules from 3 to 4 cm. in diameter. The right lung weighed 960 grams and the left 700 grams. The cut surface was dark red and large amounts of serosanguineous fluid exuded on compression. The mucosa of the tracheobronchial tree was injected and a large amount of bloody, mucoid fluid was present within the trachea and bronchi. The mucosa of the pyloric end of the stomach, duodenum, jejunum and ileum was injected. Examination of the head was restricted.

Routine specimens from the organs were fixed in Zenker's fluid and a 10 per cent solution of formalin, U.S.P. and stained with phloxine-methylene blue, phosphotungstic acid-hematoxylin and Mallory's aniline blue stain for collagen.

Microscopic Examination: Sections of the heart showed scattered, filariform larvae surrounded by focal accumulations of lymphocytes in the pericardium and in the interstitial tissue of the myocardium (figure 1).

The pleura showed many filariform larvae lying in the subpleural areolar tissue and pleural lymphatics (figure 2). The alveoli contained precipitated protein, many

red cells and filariform larvae, some of which were surrounded by polymorphonuclear leukocytes, desquamated epithelial cells and lymphocytes (figure 3). The submucosal and adventitial lymphatics of the trachea contained similar parasites without any surrounding cellular infiltrate (figure 4). Parasites were present in the sinuses of the tracheobronchial lymph nodes.

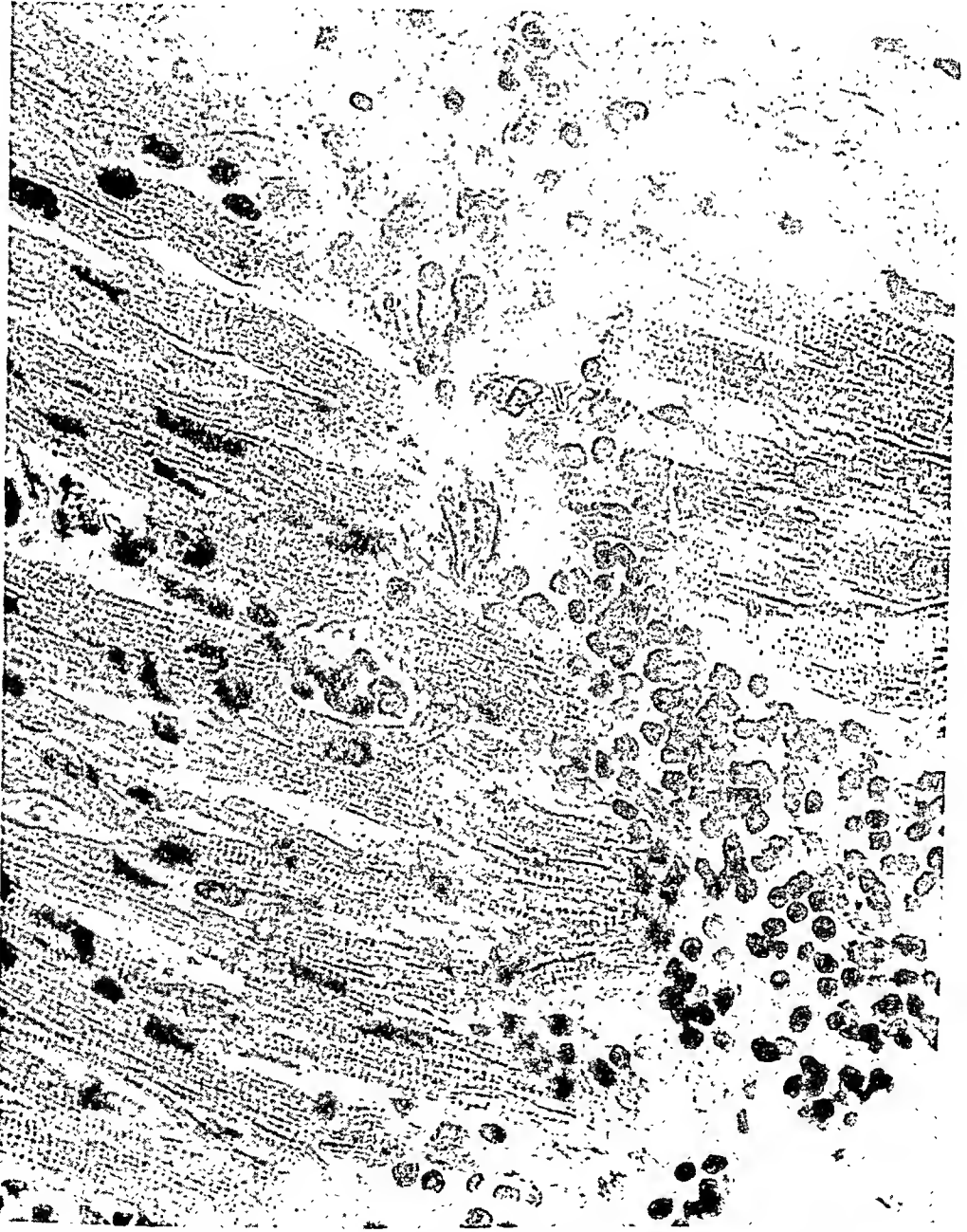


FIG. 1. Photograph of portion of filariform larva in myocardium with surrounding infiltrate of lymphocytes.  $\times 400$ .

Filariform larvae were found in several portal areas in the liver and were surrounded by an inflammatory infiltrate consisting of lymphocytes and a few polymorphonuclear leukocytes. Filariform larvae were also found in the submucosal and subserosal connective tissue of the gall-bladder.

The stomach and small intestine were heavily infested with parasites. In the gastrointestinal tract the mucosa showed infected areas alternating with uninfected areas. In the stomach adult worms were present in the gastric glands and a few were seen in the stroma between the glands. Ova were seen between the epithelial cells

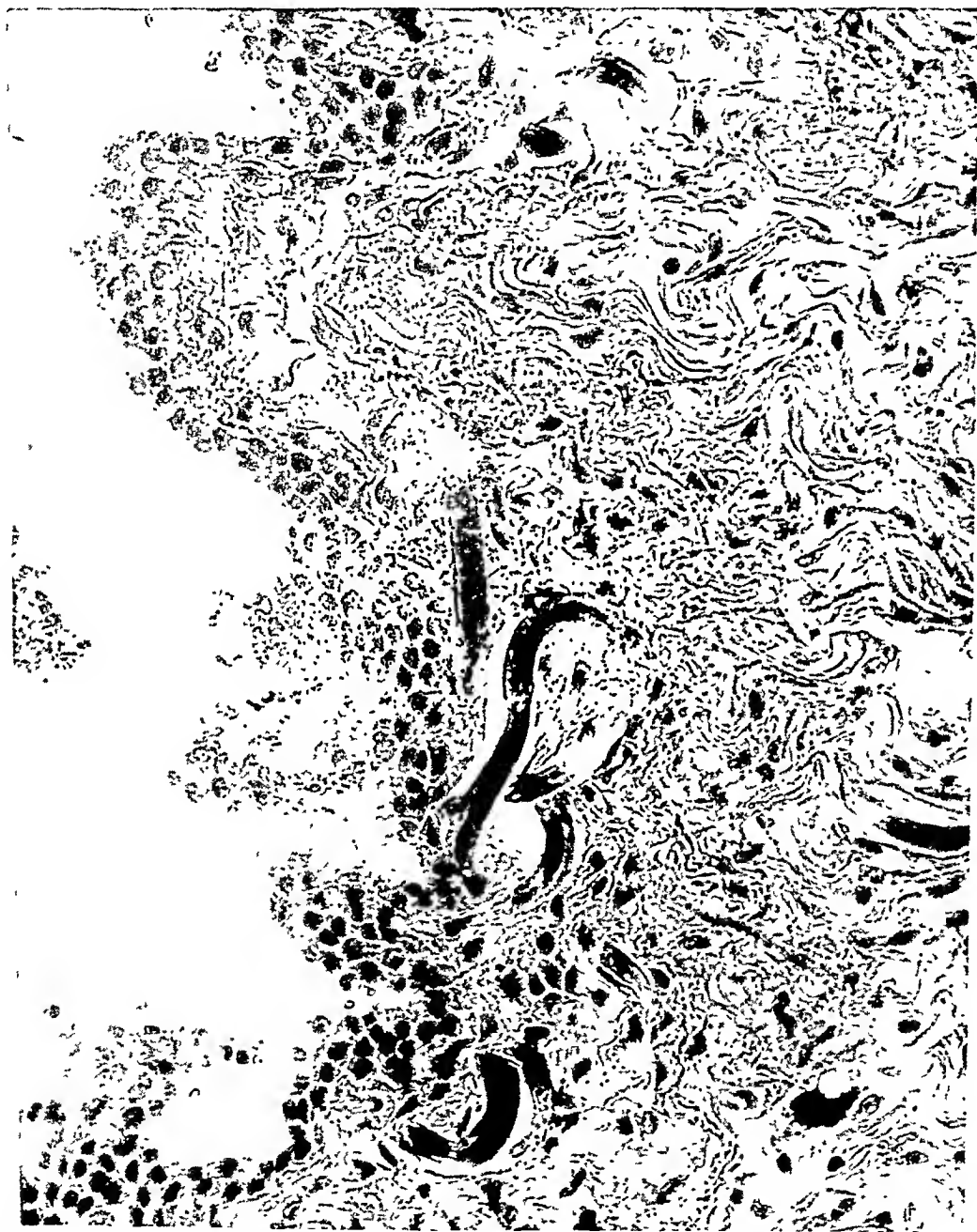


FIG. 2. Photograph showing filariform larvae lying in the subpleural connective tissue.  
× 300.

in the more superficial portions of the glands. The lumen of the stomach contained numerous rhabditiform larvae and adult worms and many polymorphonuclear leukocytes. No parasites were seen in the muscular layers of the stomach wall.

In the duodenum the infestation was more massive, with numerous adult worms lying deep in the crypts and in the interglandular stroma (figure 5). Some of these lay perpendicular to the long axis of the crypts cutting across several glands. In addition, ova (figure 6), embryos (figure 7) and rhabditiform larvae were present in

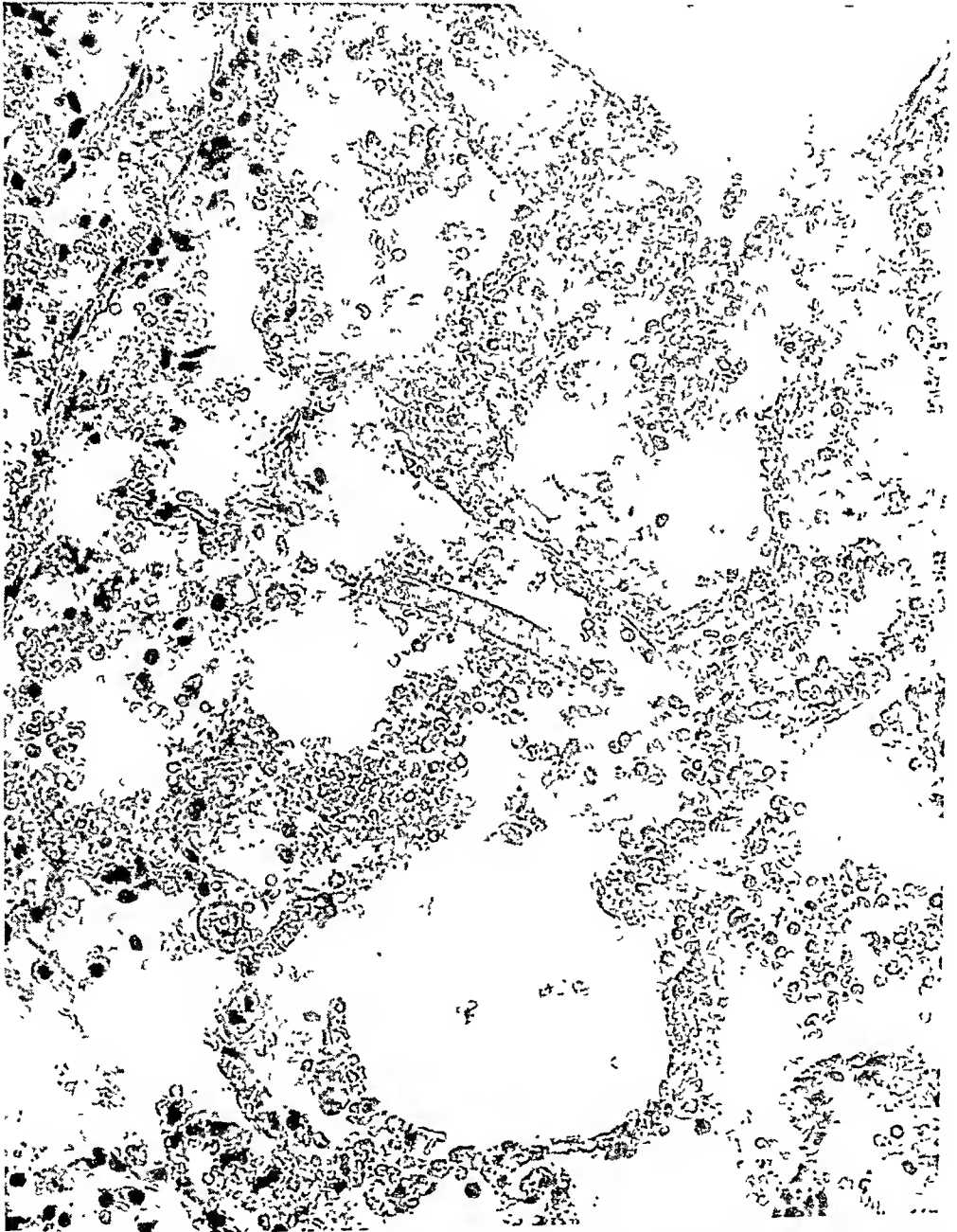


FIG. 3. Photograph of filariform larva lying in an alveolar space. Note the red blood cells scattered throughout the alveolar spaces.  $\times 300$ .

the lamina propria and between the epithelial cells which form the lining of the crypts. The epithelium surrounding the adult worms, embryos and ova appeared compressed or desquamated and some of these forms of the parasite were surrounded by a mem-

brane of flattened epithelium and a zone of plasma cells and lymphocytes (figure 7). The larvae in the mucosa and the submucosa were surrounded by an exudate which differed only in that it contained moderate numbers of eosinophiles. The submucosa contained a few filariform larvae. All of the forms of the parasite were observed

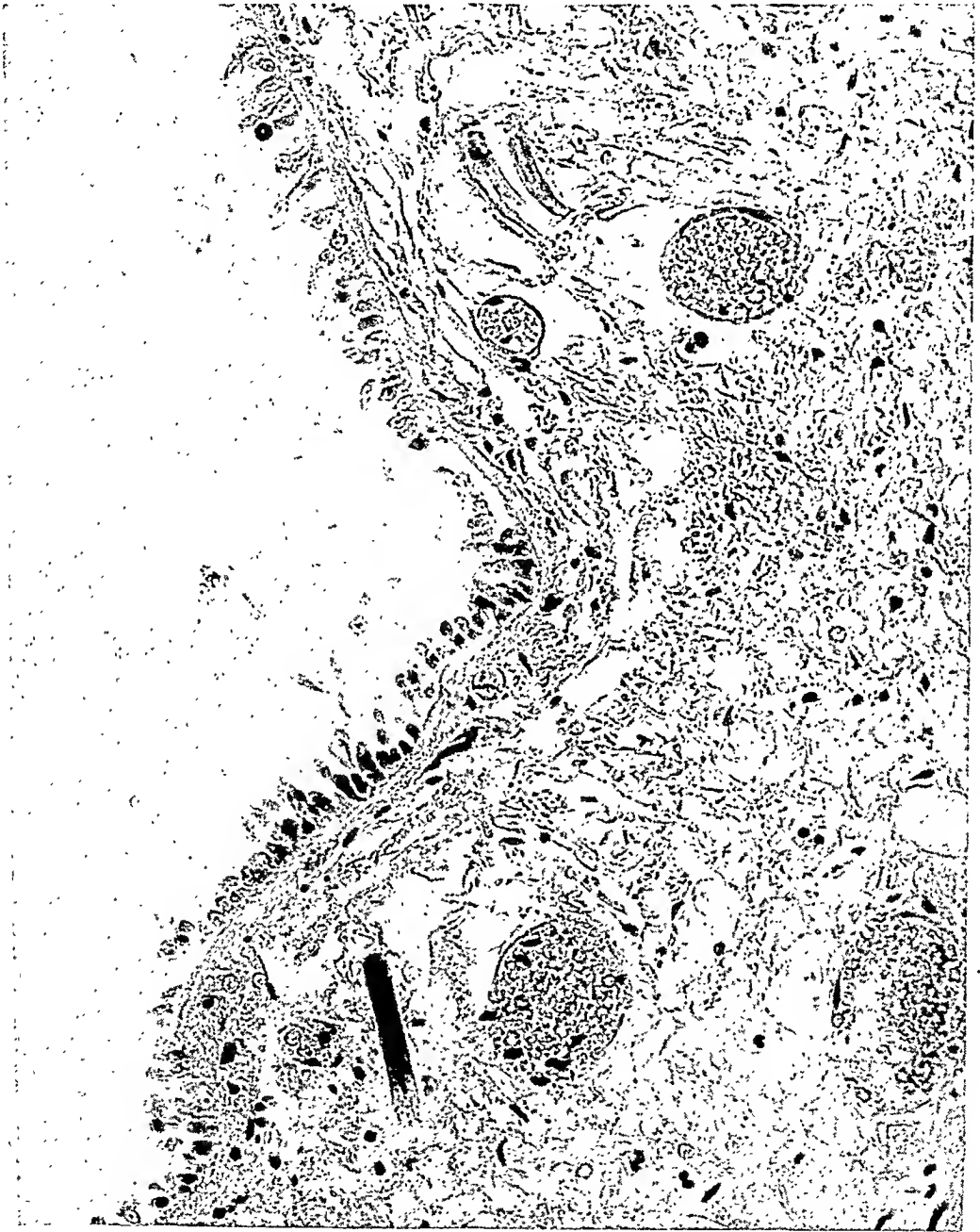


FIG. 4. Photograph of filariform larvae lying in the submucosa of the trachea. Note absence of any inflammatory infiltrate.  $\times 200$ .

within the lumen of the duodenum while none were seen in the muscularis or serosa.

All forms of the parasite were present in the jejunum, but fewer adult worms were noted and rhabditiform and filariform larvae were especially numerous. The latter were found in the mucosa, the submucosa, muscularis, subserosal lymphatic

and connective tissue. Many of the parasites in the submucosa and muscularis had not caused an inflammatory reaction. Several, however, were surrounded by granulomatous nodules consisting of mononuclear phagocytes, a few lymphocytes and foreign body giant cells. The larvae in the center of these lesions were densely eosinophilic. Similar nodules were found in the mesentery (figure 8).

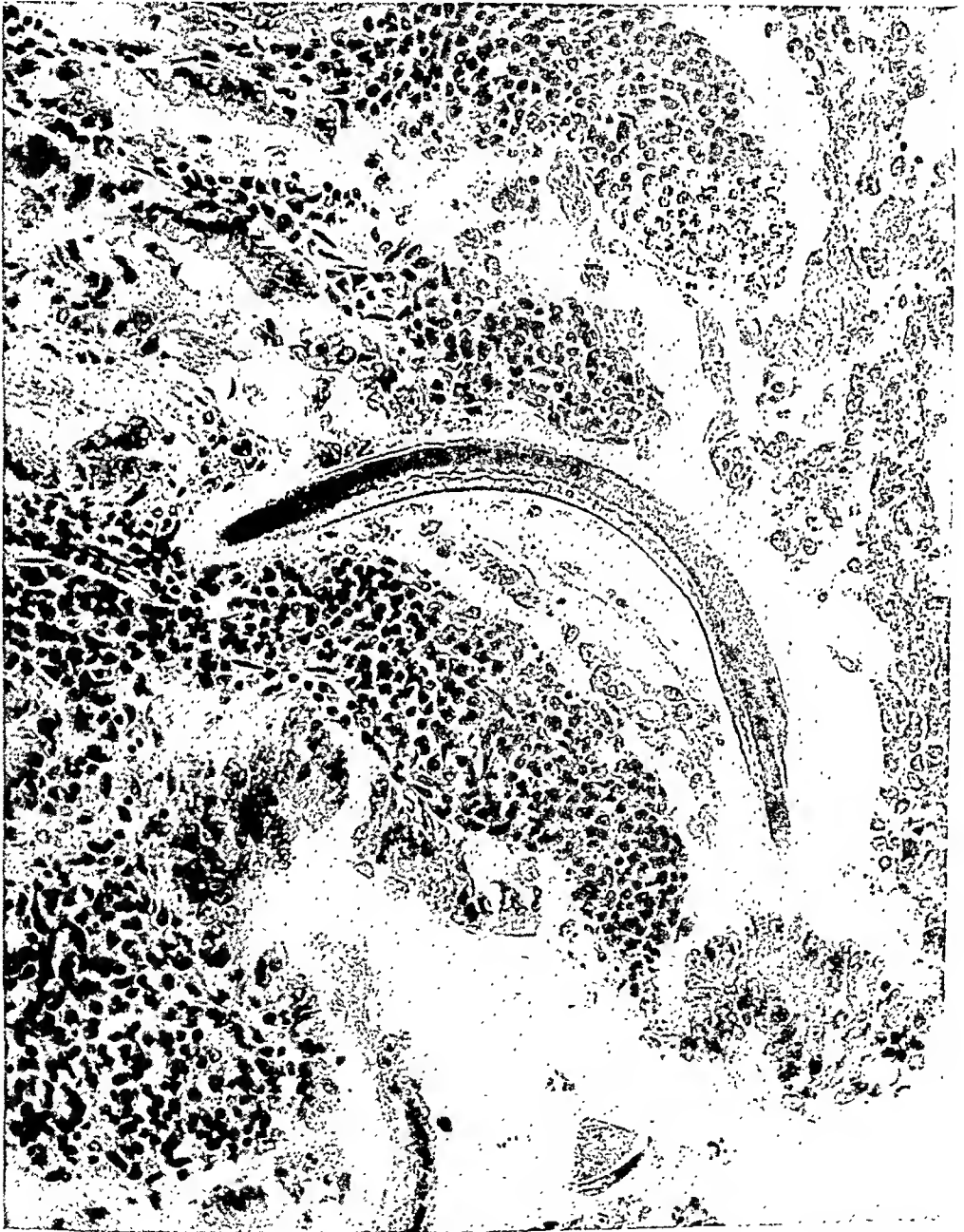


FIG. 5. Photograph of adult female worm lying in a glandular space in the duodenum.  
× 400.

Filariform larvae were noted in all layers of the ileum but no other forms of the parasite were found. They were present in the lymphatics, connective tissue and fat of the mesentery of the ileum (figure 9). Most of these parasites showed no



surrounding inflammatory exudate but macrophages, lymphocytes and plasma cells were found around a few.

A few filariform larvae were found in the subserosal lymphatics of the colon and appendix and in the submucosa of the appendix.

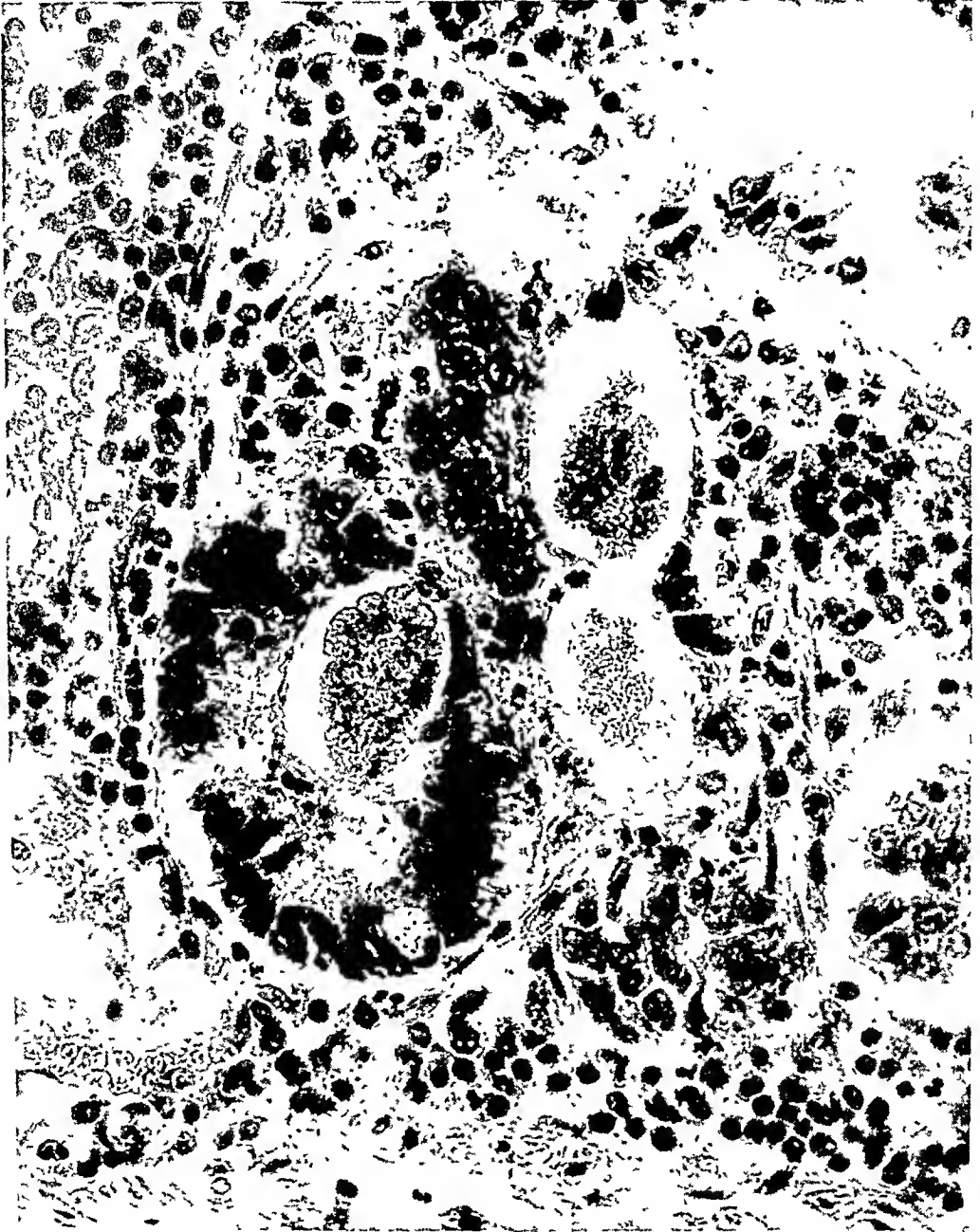


FIG. 6. Photograph of *Strongyloides* ova lying in crypts and interglandular spaces of duodenum.  $\times 400$ .

The mesenteric lymph nodes contained many filariform larvae in the perinodal lymphatics, the sinusoids and pulp. The sinuses contained increased numbers of macrophages, eosinophiles and polymorphonuclear leukocytes. Foreign body giant

cells phagocytizing fragments of larvae were seen in the sinusoids and pulp of the nodes.

Sections of the mediastinal tumor showed large lobules separated by dense fibrous bands. These lobules were composed of cords and clusters of spindle-shaped cells

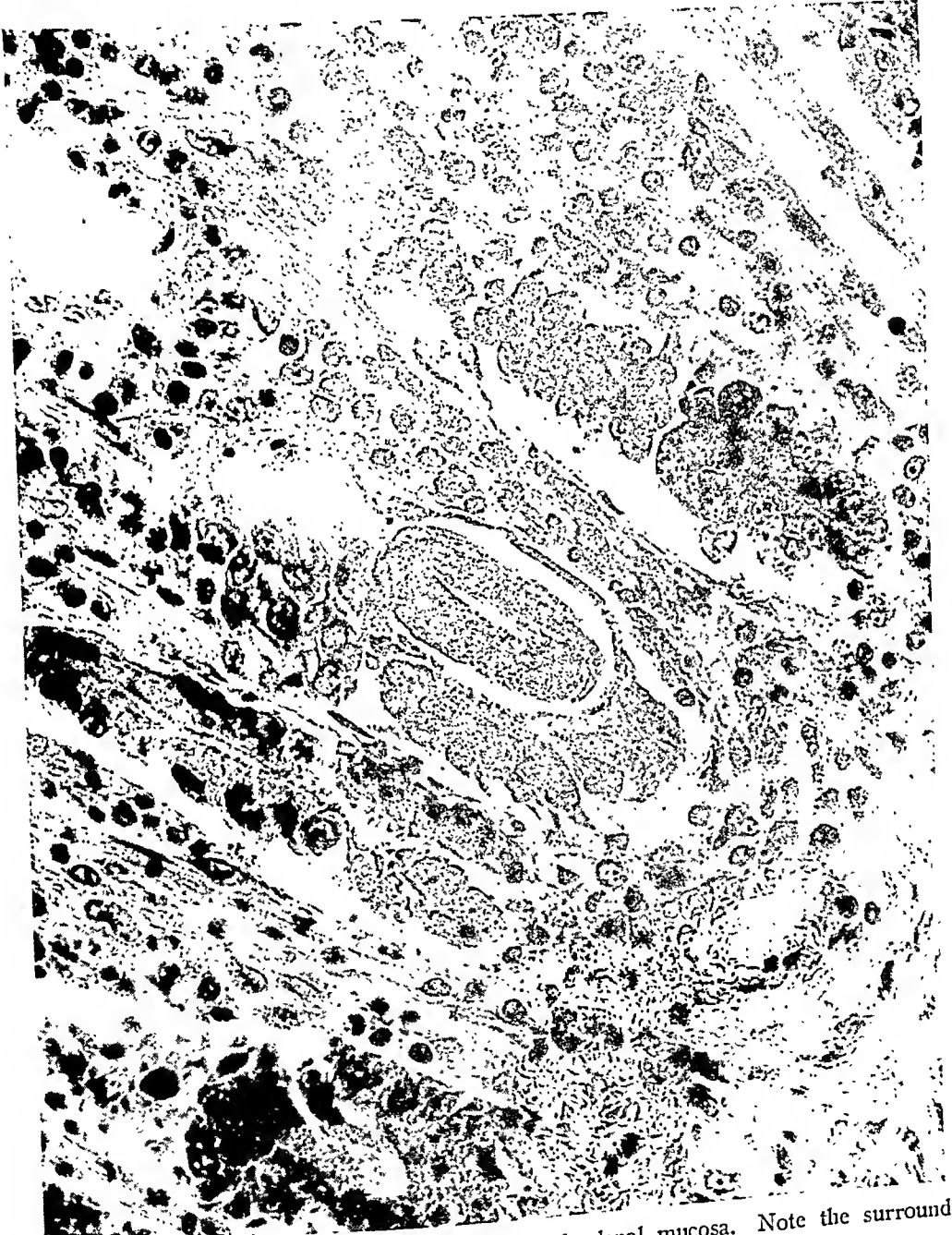


FIG. 7. Photograph of *Strongyloides* embryo in duodenal mucosa. Note the surrounding capsule of flattened epithelium.  $\times 400$ .

with scant cytoplasm and elongated nuclei containing finely dispersed chromatin. Many of the cells were lined up around thin-walled vascular channels. The cells were uniform in appearance and no mitoses were seen.



Anatomic Diagnoses: (1) *S. stercoralis* infestation involving the stomach, small and large intestine, appendix, mesentery and mesenteric lymph nodes, lungs, trachea, heart, liver and gall-bladder. (2) Pulmonary hemorrhage and edema (diffuse). (3) Benign mediastinal tumor, ? thymoma or endothelioma.

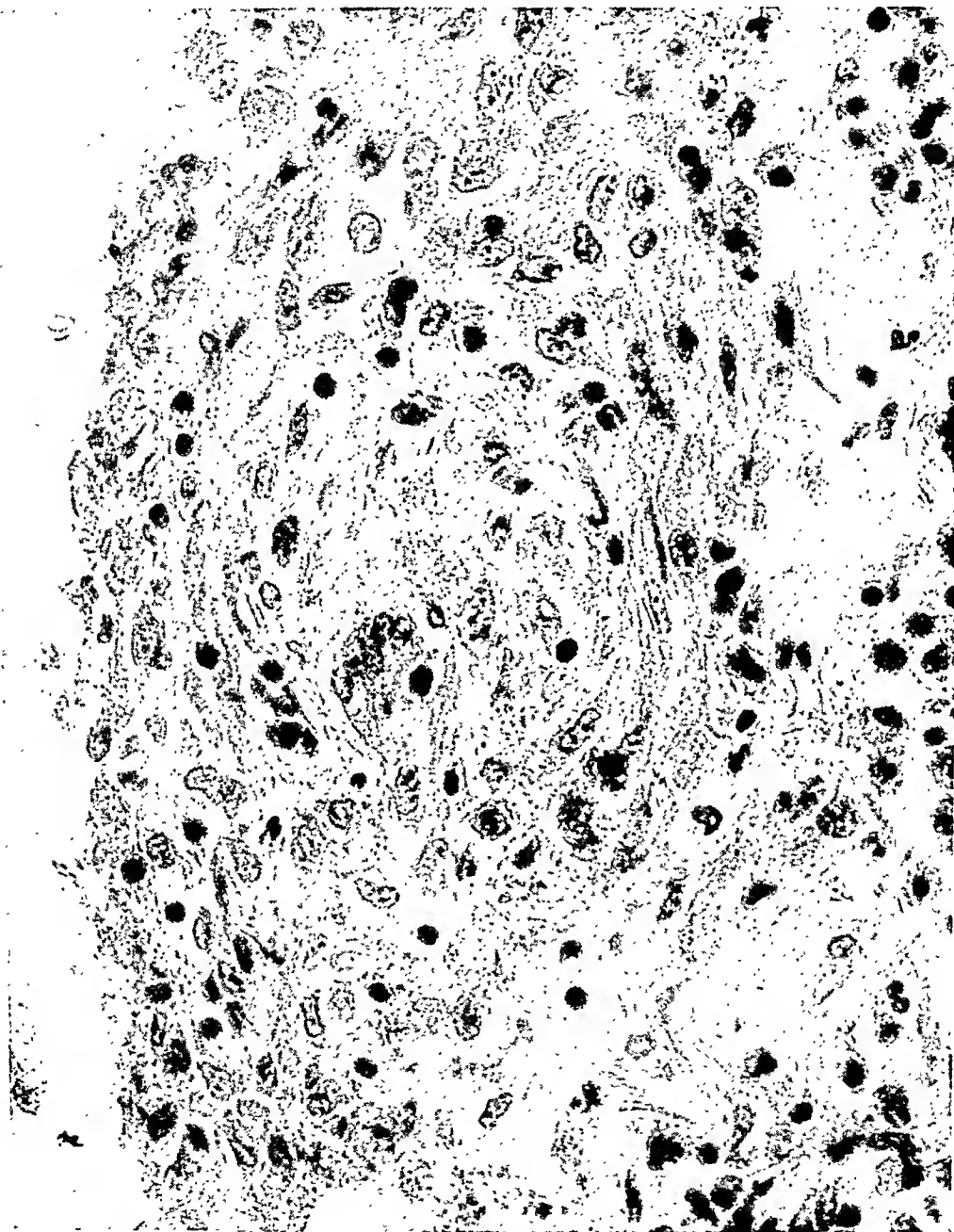


FIG. 8. Photograph of granulomatous nodule in mesentery.  $\times 400$ .

#### BIOLOGY OF *S. Stercoralis*

*Geographical Distribution.* Although cosmopolitan in distribution, this parasite is much more common in warmer areas where its incidence parallels

that of hookworm. In the western hemisphere Strong<sup>5</sup> reports the disease as common in Brazil, Panama (23 per cent), Colombia (16 per cent) and Puerto Rico (35 per cent). In the southern part of the United States Hinman<sup>6</sup> found that the incidence varied from 1 to 5 per cent, while Faust



FIG. 9. Photograph of filariform larvae in connective tissue of mesentery. Note absence of surrounding inflammatory response.  $\times 300$ .

found that 4 per cent of the hospital patients in New Orleans were infected. Cases of the disease are reported sporadically from more northern regions of the United States, the most noteworthy being those of Ginsburg<sup>7</sup> who

found a case in western Pennsylvania, and Senseman<sup>8</sup> who studied a patient in Rhode Island. Other cases have been reported but for the most part these have been patients who at one time lived in the tropics, or in other areas where the disease is endemic. Cadham<sup>9</sup> reported a case in a Canadian who had never left the vicinity of Winnipeg, but inasmuch as she was a nurse the possibility of contact infection must be considered. Shikhobalova and Semenova<sup>10</sup> discuss the presence of the disease in Russia and state that the climate is not incompatible with the existence of the disease. They emphasize that the infestation is most common in soldiers, many of whom spent time at the front under conditions which favored the spread of the disease.

*Morphology.* The ova of *S. stercoralis* closely resemble hookworm ova but are smaller, measuring 50 to 58 micra in length and 30 to 34 micra in width. They are frequently seen joined together by the remnants of the maternal uterus. They are found in the stool only during a bout of violent diarrhea or after purgation.

The rhabditiform larvae are from 200 to 250 micra in length and have a short buccal cavity leading into a double esophagus.

The filariform larvae are much longer and thinner than the rhabditoid larvae. They measure 700 micra in length and have a simple straight esophagus and intestine. Lowe and Lancaster<sup>11</sup> state that the tail is notched and Faust<sup>12</sup> found that filariform larvae in cases exhibiting the hyperinfective cycle were stunted and had notched tails. Other observers describe a sharp-pointed tail.

The parasitic females are difficult to see because of their small size and transparency. They measure 2.5 mm. in length by 30 to 75 micra in width and have a filariform esophagus one-fourth the body length. A double uterus in which ova may be seen lies in the posterior two-thirds of the body. The vulva opens on the posterior third of the body.

The adult male is shorter than the female, being about 0.7 mm. long and 40 to 50 micra wide. It has a rhabditoid esophagus and its tail is curved ventrally. In this ventral curve can be seen the copulatory spicules and the gubernaculum.

*Life Cycle.* The life cycle of *S. stercoralis* resembles that of the hookworm. The mother worm burrows into the mucosa of the gastrointestinal tract, produces ova by means of parthenogenesis or by hermaphrodesis (a point upon which helminthologists are not agreed) and deposits them in the crypts of the mucosa. There the ova develop into rhabditiform larvae (non-infective form) which migrate into the intestinal lumen. According to Ash and Spitz,<sup>13</sup> there are four variations in the cycle from this point onward.

1. The *indirect* or *sexual* cycle in which the rhabditiform larvae originating from a fertilized female are passed in the feces and develop into the "free living" females and males. These forms then copulate and the female lays ova in the feces which develop into rhabditiform larvae. The rhabditiform larvae moult and become filariform larvae (the infective form). These either penetrate the skin of the host or are ingested. After the penetration

of the skin, the filariform larvae enter the venous system and pass through the blood stream to the lungs where they escape into the alveoli and bronchi and are then coughed up and swallowed. During this passage they develop into the adolescent forms and in the alimentary canal they become adult worms and the females attach themselves to the intestinal mucosa. Under suitable environmental conditions the filariform larvae may mature and several cycles may occur outside the host.

2. The *direct* cycle in which the rhabditiform larvae are passed in the feces and develop directly in 24 to 48 hours into filariform larvae without first going through an adult phase.

3. The *direct* cycle in which the rhabditiform larvae become filariform larvae in the intestine. These filariform larvae are passed in the feces and then penetrate the skin of the perianal region immediately. This cycle is referred to by Faust as *autoinfective*.

4. The *hyperinfective* type of cycle in which rhabditiform larvae are retained for a sufficient length of time in the bowel to allow development into filariform larvae. These penetrate the intestinal wall, pass through the mesenteric lymphatics or portal system and enter the systemic circulation. They circulate through the heart to the lungs, enter the alveoli, are coughed up and swallowed, during which time they are developing into the adolescent male and female forms. In the gastrointestinal tract they develop into adult worms and the females then attach themselves to the intestinal mucosa. There is a difference of opinion among helminthologists as to the validity of this hyperinfective type of cycle. Fulleborn<sup>14</sup> was unable to produce it experimentally and he concluded that the soiling of the perianal skin with the patient's moist feces provided the opportunity for the rhabditiform larvae to metamorphose into the filariform stage and to enter the body percutaneously. However, Faust and his associates<sup>15</sup> have reported that they have produced experimental hyperinfection. Faust and DeGroat<sup>16</sup> have given an excellent summary of the evidence for the hyperinfective cycle, which leaves little doubt concerning its existence.

Another minor variation may occur in the life cycle. According to Faust<sup>15</sup> larvae may remain in the pulmonary tissue where they develop into adult worms; insemination occurs and the adult females lay ova which develop into larvae.

*Length of Infestation.* One of the most important characteristics of the parasite is its ability to inhabit the human body actively for prolonged periods of time. Other parasites, such as *Trichinella* and *Echinococcus*, persist in the host for long periods of time but in the inactive encysted form. Pinworm infestation perpetuates itself through the mechanism of self-reinfection of the host and thus its persistence depends on poor personal hygiene. There are many reports illustrating the occurrence of *S. stercoralis* larvae in the feces for many years after the original infection. Both Levin<sup>17</sup> and Bodon<sup>18</sup> have reported cases in which the infestation persisted for 20 years and in Palmer's<sup>19</sup> case there was evidence of infection over a period of 30 years.

Our patient harbored the organism for at least 13 and possibly for 26 years after leaving the presumed location of original infection. Such long-continued presence of the parasite in the human body is undoubtedly maintained through hyperinfection.

The following table shows the comparative lengths of infestation in the human intestine of the various parasites which are predominantly intestinal pathogens or which at one stage in their cycle cause intestinal symptoms.

TABLE I  
Duration of Active Intestinal Infestation by Parasites

Disease	Superinfection	Average Duration	Maximum Duration
Ancylostomiasis	0	6-12 months	6 years
Ascariasis	0	8-12 months	1 year
Diphyllobothriasis	0	years	16 years
<i>Fasciolopsis buski</i> (intestinal fluke)	0	years	years
(intestinal distomiasis)			
Oxyuriasis (Enterobiasis)	+	years	years
Strongyloidiasis	+	years	30 years
<i>Taenia saginata</i>	0	years	years
<i>Taenia solium</i>	0	years	16 years
Trichuriasis	0	1-3 months	years
Trichinosis	0	weeks	54 days
Schistosomiasis	0	10 years	13 years
Amebiasis	0	months-years	20 years

Only two parasites, *Enterobius vermicularis* and *Strongyloides stercoralis*, have a super-infective type of cycle. The intestinal infestation with *Strongyloides* exists for the longest period of time.

**Viability.** Kreis<sup>20</sup> has studied the adaptability of *S. stercoralis* to a changing and suitable environment outside the host and has found it to be poorly resistant to adverse conditions. The parasite cannot withstand refrigeration nor does it live long even in moist soil. In experimental studies Kreis could not recover any parasites from inoculated soil after seven days had elapsed. He points out that most species of nematodes are protected either by encystment of ova to prevent desiccation or by production of large numbers of ova to increase the possibilities of survival, but neither is true of *S. stercoralis*. However, *S. stercoralis* may maintain itself in the soil by means of a free-living cycle and in addition the mechanism of hyperinfection makes persistence outside the host less essential for survival of the parasite.

**Pathogenicity.** The question of the pathogenicity of *S. stercoralis* has occasioned considerable controversy. Immediately following Normand's original observation in 1876, when he attributed the so-called Cochin-China diarrhea to this organism, none questioned its pathogenicity. However, with the identification of other etiological agents as a cause for severe dysentery, enthusiasm regarding the pathogenicity of *S. stercoralis* began to wane. Darling<sup>21</sup> in 1911 did not believe that *S. stercoralis* caused diarrhea but hypothesized that it might make the host more susceptible to other infections.

A. L. Levin <sup>22</sup> in 1930 believed that symptoms resulted only in those humans whose intestine was especially suited for growth of the parasite and that the major portion of the symptomatology was due to secondary bacterial infection. Ophuls <sup>23</sup> believed that intestinal symptoms developed on the basis of entrance of the organism into the intestinal wall of a sensitized person. Kreis <sup>20</sup> in 1932 stated that in his belief dysentery could occur only with the coexistence of another parasite in the patient's gastrointestinal tract. Recent observers state that *S. stercoralis* is a true pathogen. Lowe and Lancaster <sup>11</sup> describe 16 cases, nearly all of recent infection, in which other parasites were eliminated following treatment, but which continued to show definite symptoms. Lewis, <sup>24</sup> in a study of enteric infection in soldiers, found that among the patients with strongyloidiasis were more that had symptoms than there were carriers. Of the 16 cases studied 11 had definite symptoms. Hinman <sup>25</sup> found severe symptoms in 85 cases and observed that the disease is one of relapses and remissions. This latter characteristic tends to modify judgment as to the pathogenicity of the organism if the patient is seen in a stage of remission. Cadham's patient <sup>9</sup> had no other parasites and yet showed constant and rather severe symptoms. Faust, in his extensive studies of the disease, found many patients who showed definite symptoms and some with extremely severe dysentery. Shikhobalova and Semenova <sup>10</sup> found definite symptoms in all of their 29 cases and I. L. Levin <sup>26</sup> noted that although the clinical picture was variable, the disease could be severe and even fatal. The possible fatal outcome of the disease can no longer be doubted. In the cases of Ophuls, <sup>23</sup> Faust and DeGroat, <sup>16</sup> Nolasco and Africa, <sup>27</sup> Gage <sup>28</sup> and in the case reported here no other cause for death could be found. Ginsburg, <sup>7</sup> A. L. Levin <sup>22</sup> and Hartz <sup>29</sup> also report deaths in patients suffering from the disease but did not show pathological evidence that *S. stercoralis* infection caused death.

*Method of Infection.* Undoubtedly the infective (filarial) form of the parasite most often gains entrance to the body by penetrating the skin. It is possible that infection can also occur by the ingestion of infected material, the larvae penetrating either the oral or intestinal mucosa. A. L. Levin <sup>22</sup> believes that this is by far the most common method of infection. During recent years increasing attention has been paid to the possibility of contact infection. Miller and his associates <sup>30</sup> state that this mode of infection is very common. Neal <sup>31</sup> describes the disease in a man who had never been in an endemic area but who had lived in close association with a group of Chinese students three years prior to the onset of symptoms. Cadham's patient may also have been infected through contact.

*Pathology.* The parasites enter the skin by burrowing under the scales of the stratum corneum and along the hair follicles. They then go through the deeper layers of the epidermis into the corium. Although the reaction to the parasite in the skin has not been well studied in man, certain facts are suggested from animal experimentation. The reaction apparently varies

with the number of larvae used in the inoculum. Hoeppli (cited by Faust)<sup>4</sup> found that with a heavy inoculation there was severe destruction of the epithelium accompanied by an exudate of fibrin, polymorphonuclear neutrophils and eosinophiles. With a light inoculation Faust<sup>4</sup> found that the epidermis remained intact and that a fibrocytic proliferation occurred along the path of invasion. When the larvae remained viable, no inflammatory exudate was noted. However, many of the larvae died, underwent degenerative changes and were surrounded by a zone of polymorphonuclear leukocytes. Faust is of the opinion that this mild reaction to a light inoculation is the one which occurs naturally in the accidental infection of man. Although many parasites are arrested and die in the skin, some invade the venules of the corium and migrate to the lungs by way of the blood stream.

Upon reaching the capillaries of the lungs, the larvae break out into the alveolar spaces, producing hemorrhages within the air passages which are usually petechial but may be massive. The parasites in the alveolar spaces are usually surrounded by polymorphonuclear leukocytes, lymphocytes and desquamated epithelial cells. A severe, even fatal, pneumonitis may result. In some of Faust's experimental animals<sup>4</sup> the pulmonary infestation was so severe and the leukocytic response so massive that the larvae could not escape from the alveoli into the bronchi and trachea and therefore developed into the adult form in the lung. The adult females and their ova were found in the bronchial mucosa and alveoli. The larval forms then developed and the life cycle was completed in the lung. In our case the filariform larvae were found in moderate numbers in the alveolar spaces and the accompanying pulmonary hemorrhage and edema were severe and appeared to be the major cause of death. No other forms of the parasite were noted in this location. Large numbers of filariform larvae were present in the visceral pleura. It is interesting to note at this point the case reported by Froes<sup>32</sup> in which he found rhabditiform larvae in a hemorrhagic pleural effusion and also in the pericardial fluid at autopsy. Figure 2 shows the superficial location of the larvae in the pleura, from whence migration into the pleural cavity could be easily accomplished. The fact that the larvae found by Froes were rhabditiform suggests that the patient harbored the adults in the pulmonary tissue.

While migrating up the trachea the filariform larvae occasionally invade the submucosa and even the outer layers of the trachea as was demonstrated in our case. Although no cellular exudate was found around these parasites, hyperemia of the submucosa was evident on gross and microscopic examination.

In the gastrointestinal tract the adult females attach themselves to the mucosa of the duodenum and jejunum. Less frequently they are found in the stomach, ileum and colon. Rarely they are found in the mucosa of the appendix (Faust and DeGroat).<sup>16</sup> In experimentally infected animals they have been found in the mucosa of the gall-bladder. In the small intestine they burrow into the crypts of Lieberkuhn and curl upon themselves, thus

placing the genital pore near the base of the crypt. Some invade the stroma and are seen lying in the interglandular connective tissue, while others are seen lying transversely, cutting across several crypts. The adult females do not penetrate beyond the muscularis mucosae. The females deposit ova between the epithelial cells of the glands and in the interglandular stroma. These ova are most numerous near the base of the glands but they may be found in small numbers at any level of the mucosal layer. Curled up embryos and rhabditiform larvae are found in large numbers in the same locations as the ova. The epithelium of the involved crypts may be compressed or desquamated and often a thin membrane of flattened epithelium is seen encapsulating adult females, ova and embryos. The inflammatory response in the intestinal mucosa is characterized by a local eosinophilia in the areas surrounding migrating rhabditiform larvae and an increase in the number of plasma cells in the lamina propria of the involved areas. Faust<sup>4</sup> has shown experimentally that the removal of dead adult females is accomplished by large macrophages which gather just outside the encapsulating epithelial membrane surrounding the worm and then break through this capsule and phagocytize the parasite.

Microscopic study of a section of heavy infected duodenum or jejunum reveals a patchy loss of mucosal epithelium with numerous tunnel-like spaces in the supporting fibrous stroma. This honeycombed appearance is caused by the migration of the rhabditiform larvae from the lamina propria to the lumen of the bowel. The tips of many of the villi in the honeycombed areas become thickened and club-shaped. Rhabditiform larvae may be seen lying in the mucosal layer and Faust and DeGroat have demonstrated them in the process of penetration of the muscularis mucosae. The rhabditiform larvae change into filariform larvae in the submucosa and therefore are not found at deeper levels.

In addition to the mechanical damage caused by the parasites in the intestinal mucosa, there is a further destruction of the glandular epithelium apparently caused by a lytic agent secreted by the adult female. This is evidenced by a disintegration of epithelial cells with loss of nuclei and cytoplasmic borders, and is most prominent in the cells near the head of the adult female.

As in our case, when the hyperinfective cycle exists, filariform larvae may be found in the submucosal, muscular and subserosal layers of the jejunum, ileum, colon and appendix. Many larvae in these regions cause no inflammatory response but others produce a tubercle-like lesion. This granulomatous lesion contains a fragment of larva in its center surrounded by mononuclear phagocytic cells, lymphocytes and frequently by large foreign body giant cells. In our case these granulomatous nodules were most numerous in the lamina propria and submucosa of the jejunum and ileum. As Nolasco and Africa<sup>27</sup> found in their case, many of these "pseudotubercles" were adjacent to or surrounded disintegrating larvae.



Although the large bowel is not usually severely involved Nolasco and Africa reported a case in which there were small "polyps" in the cecum. These "growths" were found histologically to be small organizing submucous abscesses in connection with the base of dilated glands of Lieberkuhn.

Filariform larvae are seen in large numbers in the connective tissue spaces and in the lymphatics of the mesentery. Faust and DeGroat<sup>10</sup> emphasize that it is unusual to find inflammatory cells in the vicinity of the larvae. However, in our case several of the larvae in the mesentery were surrounded by a zone of macrophages, lymphocytes and plasma cells and several of the previously described granulomatous nodules were seen. Hartz' case<sup>20</sup> is similar to ours in this respect.

In cases exhibiting the hyperinfective cycle, filariform larvae are found in enlarged mesenteric nodes (Ophuls<sup>23</sup>, Faust and DeGroat<sup>16</sup>). The larvae may be seen in the perinodal lymphatics, the sinuses and the pulp. In our case large foreign body giant cells were phagocytizing fragments of larvae in the pulp and sinuses. The sinuses were packed with macrophages, polymorphonuclear neutrophils and a few eosinophiles. There was an increase in the amount of lymphatic pulp tissue but no hyperplasia of the germinal centers.

Filariform larvae are occasionally found in the liver<sup>10, 27</sup> where they lie in the portal areas. The exudate surrounding them in this location varies. Faust and DeGroat found an eosinophilic infiltrate in their case, while in ours only an increased number of lymphocytes and a few polymorphonuclear leukocytes were noted. As exemplified by our case, filariform larvae may also be found in the gall-bladder where they lie in the subserosal lymphatics and connective tissue spaces.

In a chimpanzee which died of a massive infection with *S. stercoralis*, Blacklock and Adler<sup>33</sup> found larvae in the pericardium. They were present in the pericardium in our case and also in the interstitial tissue of the myocardium. An infiltrate of lymphocytes surrounded them but there was no anatomic evidence of injury to the cardiac muscle fibers. As far as we can ascertain no previously reported case includes similar involvement of the heart.

Experimentally the brain and kidneys have shown evidence of invasion by larvae. Fulleborn<sup>14</sup> observed hemorrhages in the glomeruli and tubules in experimentally infected animals. However, in man, although parasites have been found in the urine<sup>34, 35</sup> parasites have not been found histologically in the kidney. Likewise Faust found brain hemorrhages in several of his infected dogs, but there has been no similar observation in the human host.

Several references are made in the literature to tumor formation in strongyloidiasis. The chimpanzee studied by Blacklock and Adler had a tumor in its cecum. This was evidently not an epithelial tumor but consisted of granulation tissue containing parasites. Berk<sup>36</sup> mentions the possibility of tumor formation and refers to the general discussion by Hoepli<sup>37</sup>

concerning tumor formation in various kinds of parasitic disease. However, Hoeppli does not include strongyloidiasis in his discussion. The case of Nolasco and Africa presented many small "polyps" in the intestine which were shown to be small organizing abscesses and not true tumors. Our case presented a tumor of the mediastinum of questionable type. No parasites were found in the tumor and it is felt that the tumor was not related to the parasitic infection. The only "tumors" reported in the literature as attributable to *S. stercoralis* have been granulomas.

*Clinical Picture.* Formulation of a definite clinical pattern attributable to *S. stercoralis* is extremely difficult. Variability of location in the host and variation of host susceptibility are more marked than in any other parasitic disease. The not infrequent existence of a long latent period between infection and the development of symptoms presents a particular problem. The frequent association of *S. stercoralis* with other parasites adds to the complexity of the clinical picture. The problem can best be approached by following the path of the parasite through the body.

Within 24 hours after penetration of the skin by the infective form a marked pruritic erythema, perhaps depending in degree on the presence of previous sensitization, may appear at the site of entry. This rash is comparable in pathogenesis and appearance to the "ground itch" of hookworm. A short time later, usually within 24 to 48 hours, the larvae pass through the lungs and often give rise to transitory pulmonary symptoms. (Severe pulmonary symptoms are usually due to a hyperinfective cycle with marked and diffuse involvement of the lungs.) When the organism enters the gastrointestinal tract it finds a habitat favorable for longer survival and is able to cause more marked changes. Symptoms arising on the basis of these changes tend to be more specific but even here there is great variation in the type and degree of response with few features that aid in the differentiation of strongyloidiasis from other intestinal parasitisms. The point to be emphasized is that *S. stercoralis* can and frequently does cause severe intestinal disturbances. It is unfortunate that so many studies of the disease have of necessity been made on patients who harbored other parasites.

Certain organs other than the skin, lungs and gastrointestinal tract may become involved and give rise to symptoms. The reports suggesting infestation of the gall-bladder and biliary tract are not infrequent. The presence of renal involvement with the appearance of *S. stercoralis* larvae in the urine, as demonstrated experimentally by Fulleborn,<sup>11</sup> is partially paralleled in the human by a case described by Whitehall and Miller<sup>35</sup> who found larvae in the urine of a serviceman. However, this patient had urinary symptoms prior to his arrival in an endemic area. Faust<sup>4</sup> has described experimentally developed central nervous system lesions in the dog and suggests that such involvement in the human may occur and give rise to symptoms.

No clear-cut delineation of the clinical course can be made from an analysis of the reported cases. For the purpose of clarification, various

clinical findings stressed by different authors will be discussed briefly with emphasis on those that are more frequent and of greatest help in diagnosis.

*Diarrhea* is seen at some time during the course of all cases that are clinically diagnosed. Shikhobalova and Semenova report its presence in nearly all of their 29 cases. It may be mild or very severe.<sup>11, 12</sup> Although the diarrhea may be constant, it is usually intermittent. The presence of occult blood is a nearly constant finding if the diarrhea is severe, and according to Hinman<sup>25</sup> and Simpson<sup>38</sup> the stools may be grossly bloody.

*Abdominal pain and tenderness* have been particularly stressed by Hinman<sup>25</sup> and a study of other clinical reports reveals that these findings are not infrequent. In Hinman's series of 85 cases abdominal pain was the chief complaint in 44. The pain was most often generalized, epigastric or right-sided. Abdominal tenderness was present in 29 of the patients.

*Constipation* was found by A. L. Levin<sup>22</sup> to be the most frequent symptom in the average patient. It is usually mild in degree and of varying duration. Faust<sup>12</sup> lists constipation alternating with mild diarrhea as a frequent finding.

*Pulmonary signs and symptoms* have been described by Berk.<sup>36</sup> This author believes that *S. stercoralis* is a frequent cause of transient pulmonary infiltration and reports two cases showing such a complication. He concludes that this disease should be considered in any patient who has in addition to gastrointestinal complaints dyspnea, cough or hemoptysis. Lowe and Lancaster<sup>11</sup> have noted pulmonary symptoms in seven of 16 patients studied and stated that pulmonary involvement is more common in strongyloidiasis than in hookworm disease. However, in Hinman's series of 85 cases, only two had cough and signs of bronchitis. It is of interest that Gage<sup>28</sup> reports the recovery of the larvae of *S. stercoralis* from the sputum of a patient believed to be suffering from tuberculosis, and Froes<sup>32</sup> found rhabditoid larvae in the pleural effusion of his patient. Other reports suggesting pulmonary involvement are available and it appears that infestation of the lungs (especially in hyperinfected patients) is more frequent than is usually stated.

*Dyspepsia* was described in five of 16 carefully controlled cases reported by Lowe and Lancaster.<sup>11</sup> Vague abdominal distress, heartburn and gaseous discomfort are frequently associated with the disease.

*Jaundice* or other evidence of biliary tract involvement has been reported so frequently in association with *S. stercoralis* as to invalidate the possibility that it is an incidental finding. Eight of Hinman's patients had marked right upper quadrant tenderness and several others were admitted to the hospital with a diagnosis of cholecystitis. Levin mentions that several of his patients showed a picture of "biliary toxemia." Nisbet<sup>39</sup> believed that the obstructive type of jaundice in his patients was due to the presence of *S. stercoralis* organisms in the bile ducts and v. Engle<sup>40</sup> discussed a case with the clinical features of acute gall-bladder disease. Bodon<sup>18</sup> reports a case

with recurrent attacks of right upper quadrant pain, tenderness and jaundice that came to operation three times and in each instance no cause for the symptoms other than strongyloidiasis was demonstrated.

*Urticaria and edema* may be seen at any time during the course of the disease, and according to Simpson<sup>38</sup> these symptoms are not infrequent. Recurring attacks of urticaria dominated the clinical picture in Cadham's case. It is logical to assume that these allergic manifestations occur most often in the hyperinfected individual.

*Vomiting* was found by Hinman as the chief complaint in five patients and was a feature of the disease in two of the 11 cases reported by Miller and his associates.<sup>30</sup> I. L. Levin<sup>26</sup> described vomiting as a common symptom and Senseman<sup>8</sup> noted that nausea was an important symptom in his case. Nausea and vomiting are ascribed to either reflex nervous stimulation or to direct irritation of the gastric mucosa by the parasite. In the presence of vomiting the possibility of detecting parasites in the vomitus must be kept in mind.

*Fever* has been reported by I. L. Levin<sup>26</sup> as present in all of his 12 patients but this finding has received little attention from other observers. A. L. Levin<sup>22</sup> believes that much of the symptomatology in strongyloidiasis is due to the secondary bacterial invasion of the gastrointestinal tract. If this is correct, fever should be a more constant finding.

*Colitis* as mentioned by Simpson,<sup>38</sup> *rectal ulcers* by Wagner<sup>41</sup> and *urinary symptoms* by Whitehall<sup>35</sup> are infrequent findings and consequently are of little value in diagnosis. *Psychoneurotic symptoms* are frequently noted in association with strongyloidiasis but their evaluation is difficult.

*Laboratory Findings.* The degree of eosinophilia in the peripheral blood is often used as an absolute criterion as to the presence or absence of a parasitic disease. However, in all parasitic disease, including strongyloidiasis, lack of eosinophilic response is not uncommon. Although many authors, including Hinman, Shikhobalova and Semenova, and Senseman, stress the frequency of eosinophilia, others, such as Miller, Simpson and Faust, do not consider it to be a constant finding. Faust believes that there may be an early increase in eosinophiles with a steady decline as the disease becomes chronic. Further confirmation is given to this view by the investigations of Lowe and Lancaster who, in studying 16 cases of fairly recent infection, found a pronounced and constant eosinophilia. On the other hand, a review of cases that show very severe symptoms or a fatal outcome reveals that the eosinophiles are frequently not increased and are often entirely absent from the peripheral blood stream as was true in our case.

Anemia is not a striking feature but when present is of a mild hypochromic variety. It is much less constant and much less marked than in hookworm disease.

Examination of the stool, as in any parasitic disease of the intestinal tract, is of primary importance. The ova of strongyloides are rarely seen

except after severe purging. The characteristic larvae are easily overlooked but when searched for repeatedly and with care they can usually be detected. Although many methods of stool examination have been devised, for general use the simpler methods are best. Faust advocates the use of coverslip preparations, and if the stool is negative by this method concentration techniques are utilized. Simpson makes a small depression in the fecal mass, places therein a small amount of water and incubates for 24 hours. The larval forms pass into the water where they can be seen with the 16 mm. objective. Lowe and Lancaster are convinced of the value of stool cultures and describe in detail the procedure. Many other methods of stool examination are described in the literature, but either the technic of Faust or that of Simpson is the procedure of choice. Confusion may arise in differentiating the larvae of strongyloides from those of hookworm, especially if the stool specimen has stood sufficiently long to enable hookworm ova to hatch. The rhabditi-form larvae of *S. stercoralis* have a buccal cavity which is much shorter than that of the corresponding form of hookworm. The esophagus of the filariform larvae of strongyloides is longer than that of the corresponding stage of hookworm, usually measuring one-half the length of the body. The tail of the filariform larvae in strongyloides is often notched, according to Lowe and Lancaster, while that of the hookworm is always pointed.

Examination of duodenal washings is a very effective method of diagnosis. This procedure is of considerable value when intraduodenal medication is being given and is extremely effective in evaluating the efficacy of therapy.

Gastric analysis may reveal the presence of adult or larval forms of the parasite. Hypochlorhydria has been reported as a fairly common finding. A. L. Levin reports the presence of either achylia or mild hyperchlorhydria but Shikhobalova and Semenova found gastric acidity below normal in 9 of their 13 cases.

The search for parasites should also include studies of other body fluids. They have been identified in the sputum, pleural exudate and the urine. Vomitus should also be examined for larvae.

Roentgenographic findings in strongyloidiasis have received little attention. Garland,<sup>42</sup> in a discussion of tropical diseases of interest to the radiologist, mentions briefly that there may be changes in the small bowel suggesting ileitis and states that the presence of local infiltrating lesions in the large bowel has been reported. Berk<sup>38</sup> suggests the possibility that the "deficiency pattern" seen in hookworm infestation may also be found in strongyloidiasis.

*Diagnosis.* A suspicion of the presence of *S. stercoralis* might be aroused by the nature of the symptoms and a history of residence in an area where the disease is endemic. This suspicion would further be stimulated by the discovery of an eosinophilia. Confirmation of the diagnosis depends, however, on identification of the larvae in the feces or in other body excretions.

Repeated stool examinations or, if the results of stool examinations are questionable or negative, studies of the duodenal washings are by far the most important diagnostic procedures. Hinman<sup>43</sup> has stressed the fact that inasmuch as the female worm can produce only as many as 50 ova a day, diagnosis is dependent on the presence of a large number of females and careful stool examinations.

A practical point in diagnosis is the observation of Cordi and Otto<sup>44</sup> that strongyloid larvae rapidly disappear from stool specimens kept under refrigeration.

Differential diagnosis is not usually difficult. Confusion can arise when there is infestation with another intestinal parasite, especially hookworm. Not only are the cutaneous, intestinal and pulmonary findings similar, but also the larval forms of both parasites resemble each other closely. Their differentiation has been discussed above. As emphasized by Strong<sup>5</sup> examination of a freshly passed stool usually shows the ova of hookworm and the larvae of *S. stercoralis*. With intense diarrhea the oval forms of both parasites may be passed, but if the stool is allowed to stand for a few hours the ova of *S. stercoralis* will hatch. If there is any real doubt concerning the identity of the parasite, culture of the stool for several days will result in the development of the adult forms of *S. stercoralis*.

The finding of an acute surgical abdomen has been reported frequently in strongyloidiasis and affords a problem in differential diagnosis. Levin<sup>32</sup> reports 12 cases and states that three of the patients came to operation. Symptoms related to the biliary tract or to the appendix most often result in such surgical intervention.<sup>18, 8</sup>

Strongyloidiasis should be excluded when dealing with pulmonary lesions—especially those of subacute or chronic nature. *S. stercoralis* has been definitely implicated as one of the causative agents of pulmonary infiltration. Other parasitic diseases which may cause similar changes are discussed by Berk.<sup>45</sup> He mentions *Ascaris lumbricoides*, *Endameba histolytica*, *Fasciola hepatica* and *Necator americanus*. Tuberculosis has been reported by Gage,<sup>28</sup> chronic bronchitis by Hinman<sup>25</sup> and bronchopneumonia by Barlow<sup>46</sup> as being erroneously diagnosed when the pulmonary lesions were in fact caused by *S. stercoralis*. Careful study of the sputum in such cases may simplify the diagnosis.

Rare localization of the parasite in the host raises other differential problems. Pericarditis, pleural effusion and renal symptoms have all been attributed to *S. stercoralis*.

*Treatment.* The treatment of strongyloidiasis is far from satisfactory. Simpson<sup>38</sup> points out that a failure to appreciate the truly pathogenic nature of the parasite has resulted in a lack of interest in the development of more effective therapeutic agents. There is also a tendency to reason falsely that since *S. stercoralis* is an intestinal parasite, any good vermifuge will satisfactorily eliminate the organism. It is obvious that a non-absorbable drug

will not affect the pulmonary lesions. It is also true that in the intestine the deeply embedded females may be difficult to eliminate by the usual vermifuges. The disappearance of the larvae from the feces is not a good index of the efficacy of the therapy, for as pointed out by Faust<sup>47</sup> even in non-treated cases the larvae disintegrate while passing through the bowel and there is a gradual decrease in the egg production of the female worm. There is also the possibility that in the hyperinfective cycle larvae can leave the intestine prior to the institution of therapy and return by way of the lungs after cessation of oral medication.

Although, as in all parasitic diseases, many drugs have been used, gentian violet is by far the most popular. Faust introduced the oral use of the drug in this country in 1930 and has been its strongest advocate. In 1932<sup>12</sup> he reported cures in 45 of 47 cases and more recently he has stated that it frequently eradicates the disease.<sup>48</sup> Faust administers one grain three times a day for a total of 50 grains (16 $\frac{2}{3}$  days), repeating the course if necessary.<sup>49</sup> Hinman<sup>43</sup> reported good results with dosages of one grain three times a day for from 7 to 10 days. He did not conduct follow-up examinations. Simpson<sup>38</sup> raises considerable doubt concerning the effectiveness of the drug, pointing out that the stools may be free of the parasites and yet the infection persist in the body. Although Lowe and Lancaster<sup>11</sup> treated 13 patients with two courses of oral gentian violet, only one patient was considered cured after careful follow-up study. Lewis<sup>24</sup> found that of 10 patients diagnosed and treated overseas only one was considered cured upon return to the United States. In our case there was an initial disappearance of the larvae from the stool but they reappeared before the course of therapy had been completed.

The administration of gentian violet by stomach or duodenal tube has received increasing attention. V. Engle<sup>40</sup> reports cure by the use of a 1 per cent solution of gentian violet in a patient unaffected by previous oral medication. He noted that nausea and vomiting were frequent when the drug was given in large doses. Faust<sup>50</sup> gave 25 c.c. of a 1 per cent solution to 10 patients unaffected by oral medication and reported complete cures in all. He also found vomiting to be of frequent occurrence and suggested that slow administration of the drug by Murphy drip might lessen this toxic symptom. More recently Denhoff<sup>51</sup> reports failure of this method of therapy in five patients.

In 1936 Wagner<sup>52</sup> suggested the use of intravenous gentian violet therapy in patients with the violent hyperinfective form of the disease. Faust<sup>48</sup> recommends a similar method of treatment of foci outside of the gastrointestinal tract and states that 25 c.c. of a 0.5 per cent solution will be well tolerated. Palmer<sup>39</sup> reports a patient with *S. stercoralis* larvae in the stools who was treated by intravenous gentian violet after oral use of the drug proved ineffective. The patient died of another disease and at autopsy

no evidence of *S. stercoralis* infestation could be found. However, Lewis<sup>24</sup> failed to effect a cure by this method. It appears that this method of administration is worthy of further trial in cases with severe symptoms or when there is evidence of hyperinfection.

There are no contraindications to the use of gentian violet. Following oral medication there may be mild nausea and vomiting and the urine occasionally becomes violet. The vomiting which follows intraduodenal installation of the drug may be alleviated by lessening the speed of administration. Faust<sup>48</sup> has mentioned the possibility that medication with gentian violet may modify the indirect or hyperinfective cycles of the disease into the direct type but points out the epidemiological value of such a conversion.

Simpson<sup>38</sup> maintains that iodine solution given by duodenal tube is very effective and warrants more general use. He gives the drug as follows: the patient receives a saline purge one hour before supper and omits breakfast; 4 c.c. of compound tincture of iodine is introduced into the duodenum on alternate days until neither the feces nor the duodenal washings show any parasites or ova. An apparent value of this technic is the necessity for making the endpoint of therapy dependent on examination of the duodenal washings.

A number of other drugs have been tried and of these only thymol and dihydronal (heptylresorcinol) have any possible value.<sup>9, 38, 41</sup> Fuadin, emetine hydrochloride, tartar emetic and many other drugs have proved to be entirely ineffective.

The evaluation of any form of therapy has in the past often depended on the absence of larvae in the stools. However, the examination of stools is an unreliable index of cure. Faust<sup>49</sup> considers his patients cured only after repeated negative stools, studied by concentration methods, for three to six months after therapy. Lowe and Lancaster<sup>11</sup> consider a patient cured when he is symptom-free, has a normal eosinophile count and when cultures of his stools taken three times at weekly intervals are negative for *S. stercoralis* parasites. Simpson<sup>38</sup> considers that the only real evidence of cure is the absence of ova and parasites from the duodenal washings, and Denhoff<sup>51</sup> offers concrete evidence to support this consideration.

In summary, for the treatment of early or mild cases oral gentian violet is worthy of trial in dosage of one grain three times a day. The drug should be administered in enteric coated capsules with a one and one-half hour coating. Even if the disease is not cured, this treatment often leads to symptomatic relief. If oral medication does not prove effective, intraduodenal administration with either gentian violet or tincture of iodine should be attempted. In a patient showing severe symptoms or evidence of hyperinfection intravenous gentian violet is indicated. Twenty-five c.c. of a 0.5 per cent solution can be given on alternate days for four doses. Search should be continued for more effective therapeutic agents.



## SUMMARY

A fatal case of *Strongyloides stercoralis* is presented. The filariform larvae were found in the usual locations and in addition were found in the myocardium, lungs, trachea, liver and gall-bladder.

The clinical manifestations of this infection are variable but in general they include abdominal pain, alternate diarrhea and constipation, cough, dyspnea and hemoptysis.

Treatment with various drugs produces variable results. The best treatment to date is probably found in the use of gentian violet, given orally at first. If the infection is not cured by oral administration, intraduodenal and possibly intravenous administration should be tried.

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# THE ELECTROCARDIOGRAPHIC RESPONSE TO CHANGES OF POSTURE DURING RESPIRA- TORY ARREST FOLLOWING DEEP IN- SPIRATION OR EXPIRATION: CLINI- CAL SIGNIFICANCE \*

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IN earlier studies <sup>5, 6</sup> the simultaneous effect of changes in posture and certain respiratory phases on the electrocardiograms of healthy persons and cardiac patients was reported. Distinct differences in the three standard leads of the electrocardiograms were observed in both groups. These observations have been confirmed.<sup>3, 14</sup> These studies have been extended in the present work by including the use of chest leads. In addition, experiments on dogs have been made in order to further interpretation of the results obtained in man.

## PROCEDURE

Electrocardiograms were obtained on 65 healthy persons of both asthenic and pyknic builds and on 116 cardiac patients without congestive heart failure. Among the cardiac patients were 20 with valvular disease, 32 with coronary disease, 45 with myocardial disease, 10 with essential hypertension, five with nephritis and hypertension, and four with hyperthyroidism.

Electrocardiograms were taken in the recumbent position (*a*) during normal respiration, (*b*) in respiratory arrest after maximal inspiration (period I) and (*c*) in respiratory arrest after maximal expiration preceded by maximal inspiration (period E). The subjects were then requested to stand for 15 minutes. At the end of this period while the subjects remained standing electrocardiograms were again obtained in the manner described above. The subjects then resumed the recumbent position and electrocardiograms were obtained at intervals during normal respiration.

Three standard leads and usually two chest leads were used at the fourth intercostal space at the left border of the sternum (C<sub>2</sub>) and a little outside the apex in the fifth intercostal space (C<sub>4</sub>) with the right arm as the indifferent electrode. Slipping of the electrode was prevented by bandages. The

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electrocardiograms were taken by string galvanometer (Cambridge type), Grass, Offner, or Siemens Halsky's amplifiers.

A careful analysis of the data revealed that only three electrocardiograms are required for diagnostic purposes, namely: in the recumbent position during normal respiration, in the standing position in period E after the patient has been standing for 15 minutes, and again in the resumed recumbent position during normal respiration.\*

Evaluations of the changes in the S-T segment and in the T-wave were made in Lead I, Lead II and chest leads. Changes of the final deflection in the third lead have been generally neglected.

#### THE EFFECT OF POSTURE AND OF RESPIRATORY ARREST AFTER DEEP INSPIRATION AND EXPIRATION ON THE ELECTROCARDIOGRAMS OF HEALTHY PERSONS

*Recumbent Position.* In period I (respiratory arrest after maximal inspiration) the R-waves in Lead I were decreased; in Lead III they were slightly increased. The T-wave in Lead I and occasionally in Lead II and in the chest leads was lower or nearly iso-electric: at the same time, a bradycardia occurred.

In the next phase, period E (respiratory arrest after maximal expiration) the R-waves in Lead I were increased and in Lead III were decreased. The T-waves in Leads I and II and in the chest leads were definitely increased in height. These T-waves were sometimes even higher than those in the recumbent position under normal respiration, and were accompanied by tachycardia.

*Standing Position.* Similar electrocardiographic pictures and variations in the heart rate developed in the two respiratory periods as in the recumbent position, but these changes were more pronounced. The T-waves which were usually already slightly lower during the standing position in normal respiration became iso-electric or slightly negative in period I. However, in the following phase (period E) an increase of the T-waves in Leads I and II and in the chest leads similar to those in the recumbent position were observed.†

The electrocardiograms after the subject resumed the recumbent position (normal respiration) showed the same pattern as the original record (figure 1).

#### THE INFLUENCE OF POSTURE AND OF RESPIRATORY PHASES ON THE ELECTROCARDIOGRAMS OF CARDIAC PATIENTS

*The Recumbent and Standing Positions.* Changes in the R-waves and heart rate during the various respiratory phases were similar to those found

\* For reasons of economy, only these phases of the electrocardiogram are reported here. The intermediate steps are in my original publication.<sup>5</sup>

† In order to study whether a time element is involved in these responses, some healthy persons were requested to stand for an hour, then the electrocardiograms were taken in the same manner, but the results were the same as those taken after the 15 minute phase.

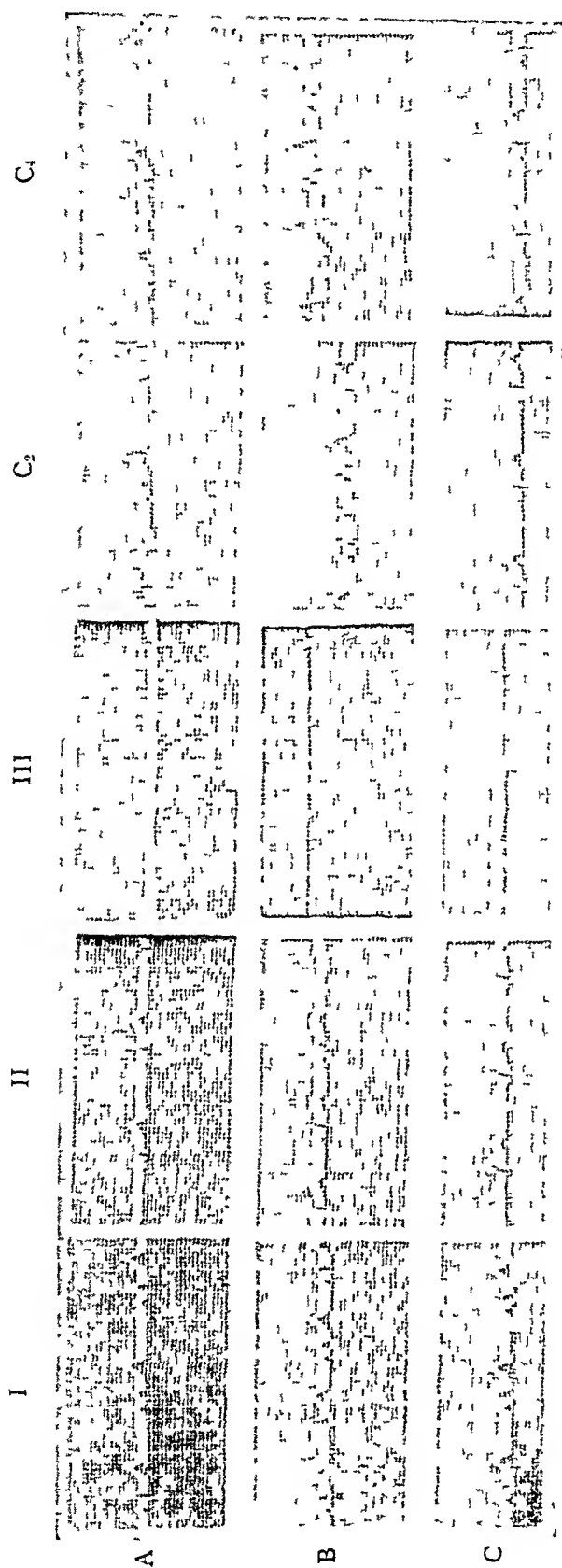


FIG. 1. From left to right I, II, III standard leads. C<sub>1</sub>, chest lead. C<sub>2</sub>, chest lead. A, electrocardiogram in the recumbent position during normal respiration; B, electrocardiogram in standing after deep expiration and C, electrocardiogram in the resumed recumbent position (during normal respiration). Healthy person, 31 yrs.

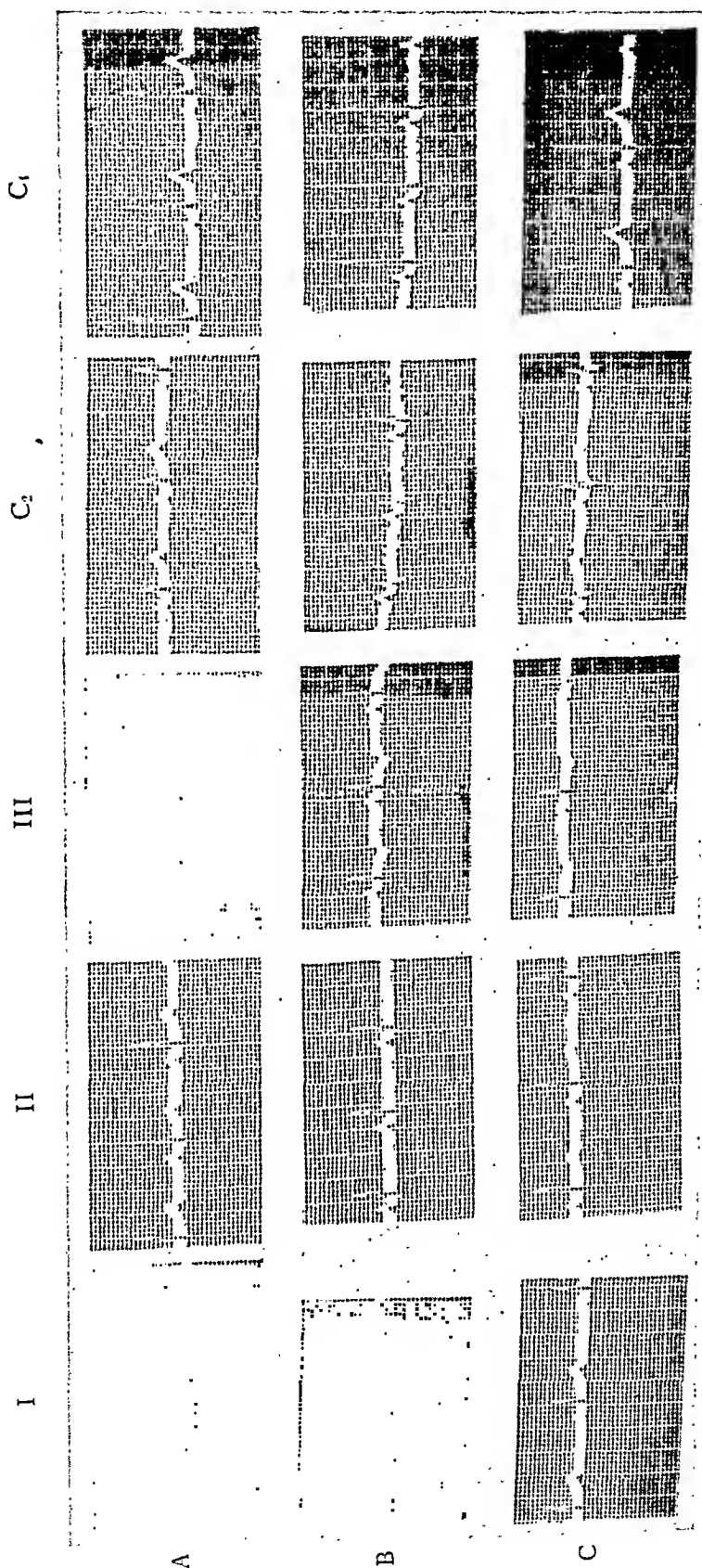


FIG. 2. Leads as in figure 1. A, B, C as in figure 1. B. T., 26 yrs. Mitral valvular disease, compensated.

in healthy persons. The alterations in the final deflection in period I were likewise similar, but the changes of the final deflection in period E in the erect posture were completely different from those of healthy persons in this phase. There could be differentiated two kinds of responses.

In 80 per cent of those cardiac patients in whom T-waves were normally positive and of slightly lower voltage in the recumbent position, changes in the electrocardiogram in standing position in period E were observed. These T-waves became iso-electric or slightly negative in Lead I, Lead II, both, or in the chest leads. Sometimes depressed S-T segments were seen

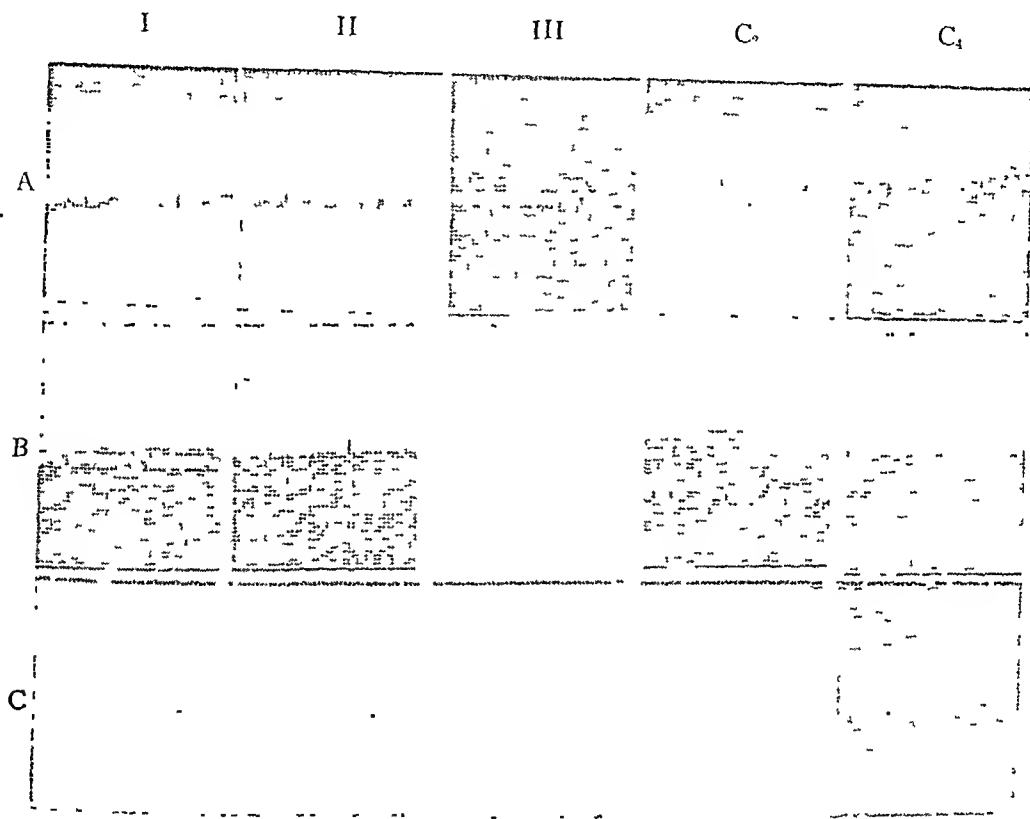


FIG. 3. Leads as in figure 1. A, B, C as in figure 1. I. D., 41 years Essential hypertension (160/116), compensated.

in these leads. Under these conditions patients with valvular disease or hypertension, for example, showed pathological electrocardiograms, where these appeared normal when taken in the recumbent position (figures 2 and 3).

In another group of patients in whom the final deflection was already pathological in the recumbent position during normal respiration, a previous negativity of these T-waves became more marked. Some S-T segments which were previously depressed showed further depression in Lead I or Lead II or in some chest leads in period E in the standing position. Sometimes the pathologic changes in the final deflections in the chest leads were



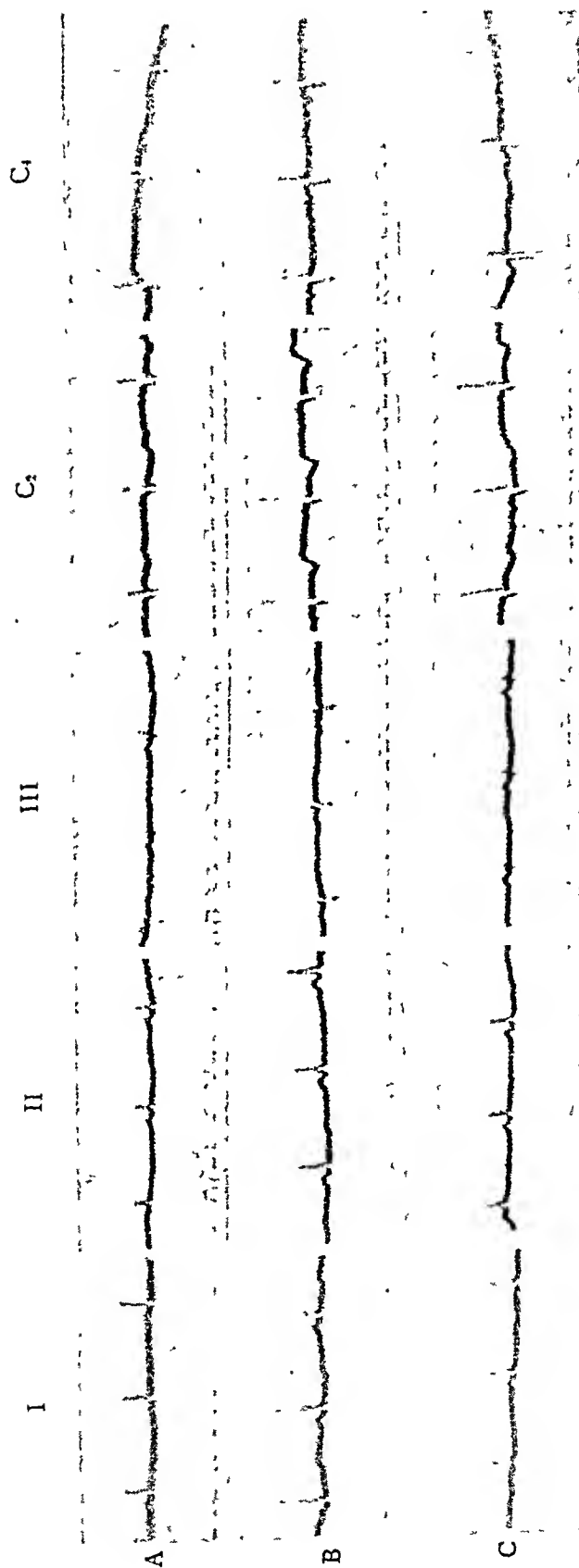


FIG. 4. Again leads as in figure 1 and A, B, C as in figure 1. I S, 61 yrs. Essential hypertension (200/112), compensated.

more pronounced than in the standard leads. About 60 per cent of the second group showed such alterations (figure 4).

In the resumed recumbent position the original normal electrocardiogram reappeared immediately in the first group (apparently patients with slight cardiac damage). In the second group of patients in whom the original electrocardiogram showed pathologic tracings, the changes in the final deflection which had occurred during the standing position disappeared more slowly, sometimes requiring 10 or more minutes.

## DISCUSSION

First of all, it was necessary to determine whether extracardiac factors such as changes in skin resistance, changes in the electrical axis due to the diaphragm variations, changes in the tone of the sympathetic and vagus nerves, and changes in the blood pressure were involved in the electrocardiogram response of cardiac patients to postural changes in the respiratory phases.

*Skin-resistance.* It might have been possible that the electrodes had slipped a little after keeping them on the skin for a long time during the different procedures. Examination of the skin resistance during all of the above-mentioned stages revealed no change.

*Change in the Electrical Axis Due to Change in the Position of the Diaphragm.* As is known the diaphragm descends greatly during a deep inspiration in the recumbent position, during normal respiration in the standing position, and especially during deep inspiration in the standing position. At the same time, changes in the form and size of the heart take place. But these postural and respiratory changes in diaphragm and heart are completely counteracted by the maximal expiration. This was proved by careful roentgen-ray investigations in normal persons and in cardiac patient.<sup>5</sup> During full expiration in standing the electrical axis is the same as during normal respiration in recumbency, as checked by roentgen-ray and electrocardiogram. It might again be emphasized that this phase (period E) is of importance for the evaluation of postural and respiratory changes in the electrocardiogram. It is clearly necessary that diaphragmatic excursion be unimpaired.

*The Vagal and Sympathetic Tone and the Blood Pressure.* In healthy persons and cardiac patients a slowing of the heart rate and a lowering of the blood pressure as well as a slight lowering of the T-waves (in Lead I or II or in one of the chest leads) occur during period I in the recumbent position. Similar changes are found in both groups of persons in period I in the standing position, but here the alterations in the T-waves are more pronounced so that they become iso-electric. This together with the bradycardia suggests a rise in the vagal tone since experiments of Rothberger and Winterberg on dogs<sup>12</sup> and my experiments on cats<sup>7</sup> have demonstrated that an increase in vagal tone is accompanied by a considerable decrease in the height of the T-waves.

During period E, healthy persons in recumbent and standing positions have an increase in heart rate, an increase in the height of the T-wave and a rise in the blood pressure up to the previous level. These changes point to an increase in the sympathetic tone, since Rothberger and Winterberg have found in dogs that a rise in sympathetic tone is associated with an increase in the height of the T-wave.\* It seems probable that central pulmonary cardiovascular reflexes<sup>7</sup> are elicited through these maximal respiratory efforts.

By maximal inspiration a great amount of blood is sucked into the chest due to the great increase in the negative intrathoracic pressure. This blood pools temporarily in the enlarged pulmonary vascular bed during the inspiratory phase, stimulating sensory pressor-receptors in the pulmonary blood vessels and eliciting pulmonary cardiovascular reflexes analogous to those from the carotid sinus.

In cardiac patients similar pulmonary cardiovascular reactions (slowing in heart-rate and lowering of the blood pressure accompanied by lowering of the T-wave in period I) can be observed. However, as it was described, the electrocardiograms of many of the patients do not show an increased T-wave in period E in standing position despite the increase in heart rate and blood pressure.

*Cardiac Factors.* Apparently not extracardiac, but cardiac factors are responsible for the difference in electrocardiographic reactions between normal and cardiac patients. According to Mayerson,<sup>17</sup> the cardiac output is decreased in the standing position as compared to the recumbent position because of the diminished venous return and the pooling of the blood in the veins of the extremities in the erect posture. Such a diminution in the cardiac output must affect the coronary blood supply since the magnitude of the cardiac output is one of the main factors in the proper filling of the coronary arteries. Thus, some degree of anoxia is produced in the heart muscle from diminished coronary circulation in all persons during the standing position. In healthy persons, this diminished coronary blood supply seems to be of no significance in period E in the recumbent and upright position because of the compensatory effect of extracardiac factors (increase in the sympathetic tone, rise in blood pressure, rise in intrathoracic pressure, etc.). But, in cardiac patients in whom the heart muscle is pathological or in patients in whom the coronary circulation is already in some way reduced by coronary disease, this additional anoxia (orthostatic anemia) is sufficient to produce pathologic electrocardiographic pictures (iso-electric T-waves or inversion of the T-wave in Lead I or II or in the chest leads, depression of the S-T segment in these leads) as in anoxia from other causes. These electrocardiographic alterations are similar to those found during the anoxemia test<sup>8</sup> or in the exercise test.<sup>2</sup>

\* It might be mentioned that Nordenfeldt and Wendkos have also shown alterations of the T-waves due to preponderance of either vagal or sympathetic tone.<sup>10, 19</sup>

Our observations are also in agreement with findings of Bartlett<sup>1</sup> who tried to induce physiologically myocardial ischemia on a tilt table. He considers this method as a test for circulatory efficiency for the selection of pilots and the diagnosis of coronary disturbances.

### EXPERIMENTS ON DOGS

Some experiments on dogs have been performed in order to investigate the influence of posture on the electrocardiogram of these animals and seem to support our observations on patients.

*Experimental Procedures.* Electrocardiograms with three standard leads were taken on 22 dogs under nembutal anesthesia in lying position, after 15 or more minutes in a tilted position of 90° (head up) and again in the recumbent position. The animals were tied on the animal board, the electrodes held firmly by bandages. The effects of the following procedure on the electrocardiographic response in different positions were also investigated: excision of the carotid sinus and the vagi and intravenous injections of various drugs (histamine, atropine, nitrites, aconite).

*Results.* In brief there were no great variations in the electrocardiogram after repeatedly changing the position except under very deep anesthesia. These findings are in agreement with the observations of Mayerson that tilting dogs from the horizontal to the upright (head up) position does not provoke any considerable cardiovascular embarrassment.<sup>17</sup>

Clamping the carotid sinus on one or both sides did not interfere greatly with the electrocardiogram in the lying or the standing position. The same was seen after cutting the vagi to eliminate the aortic depressor nerves.

Intravenous injections of histamine, atropine or nitrites did not induce considerable change into the electrocardiogram during postural changes but nitrites in doses (intravenously 33 mg.  $\text{NaNO}_3/\text{kg.}$ ) sufficient to produce a great fall in blood pressure affected the electrocardiogram of the dog in the standing position very strongly. If the dog was kept for only a few minutes in the upright position, ventricular fibrillation occurred and the dog died despite immediate return to the supine position and intravenous injection of adrenalin (figure 5).

Further, in another series of experiments different doses of aconite extract were injected subcutaneously in order to produce an artificial myocardial damage. Injections of 0.6 c.c. into a dog of 8 kg. were followed by a bradycardia and a lowering of the T-wave in Leads I and II. In the upright position, pathological electrocardiographic patterns with increased QRS intervals and iso-electric T-waves appeared. The bradycardia was much more pronounced, and the respiration stopped after the animal was kept 10 minutes in the upright position. Return to the lying position did not change the electrocardiographic picture and the other pathological signs, and the animal died a few minutes later (figure 5).

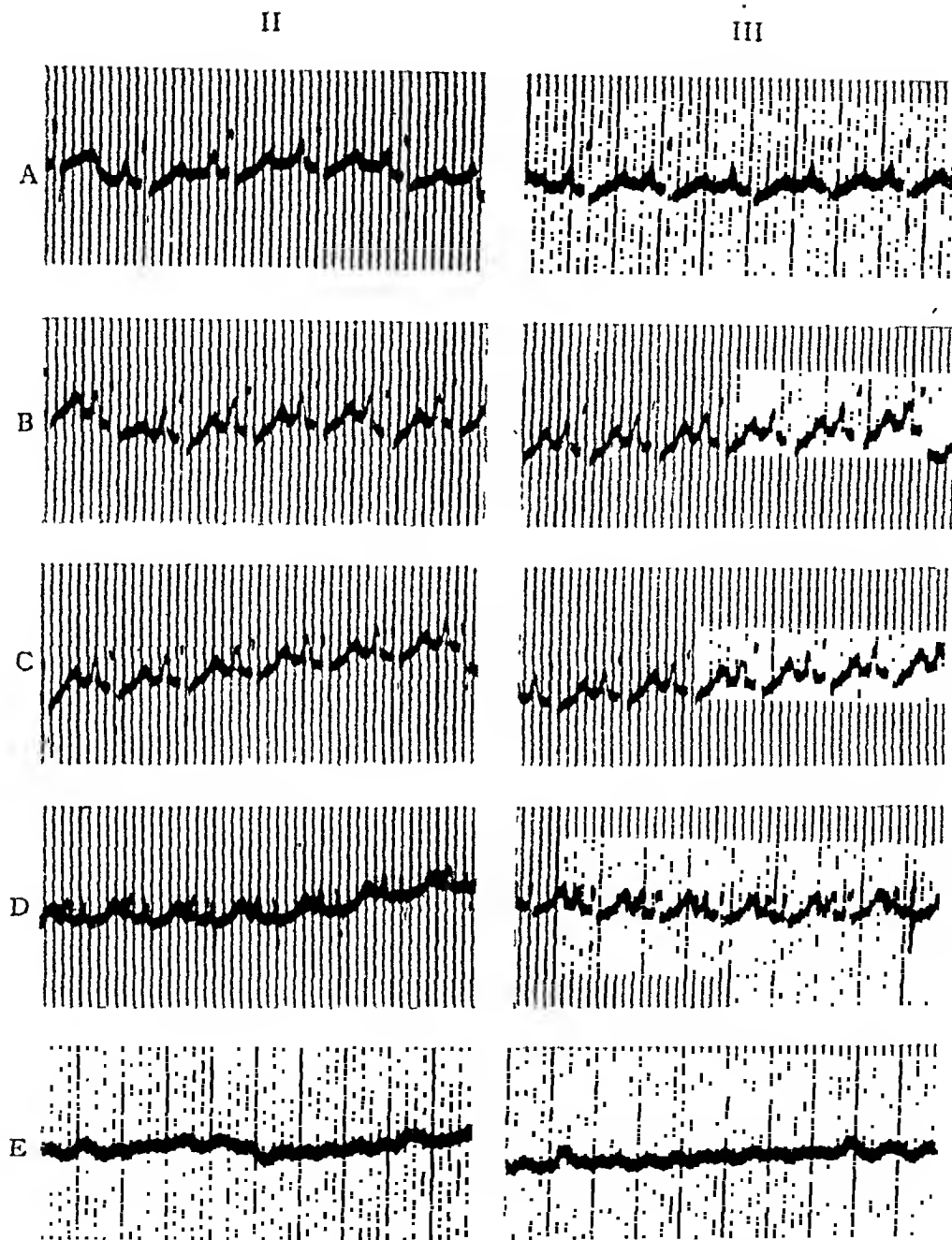


FIG. 5. Lead II, Lead III; A, electrocardiogram on recumbent position; B, electrocardiogram on standing 15 minutes; C, electrocardiogram in the resumed recumbent position; D, the electrocardiogram in the recumbent position after injection of 33 mg.  $\text{NaNO}_2$  per kg.; E, electrocardiogram in standing (after 2 minutes). Note ventricular fibrillation. Dog 10 kg. Slight nembutal narcosis.

These experiments seem to demonstrate that severe anoxia of the heart produced by great diminution of the cardiac output and of the coronary blood supply due to nitrites will provoke pathological cardiovascular responses of the dog in the upright position, whereas the lying position is not accompanied by this reaction. Further, a myocardial damage which was apparent and well tolerated in the lying position might become manifest

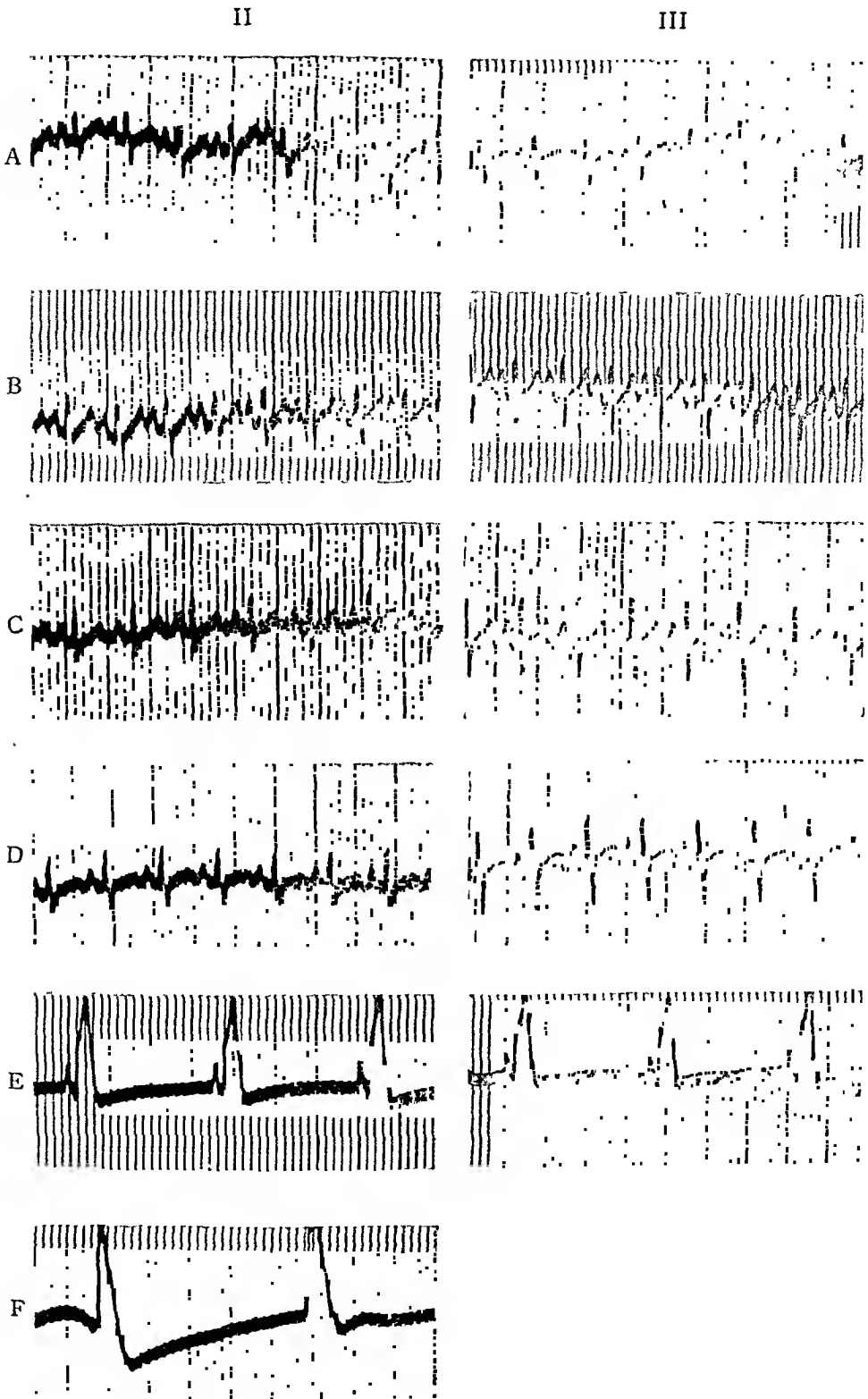


FIG. 6. II, III as in figure 5. A, B, C as in figure 5. D, electrocardiogram in the recumbent position after subcutaneous injection of 0.6 c.c. aconite extract. E, electrocardiogram in the standing position. Note the pathological electrocardiographic changes. F, electrocardiogram in the recumbent position again. Note the changed pathological electrocardiogram in Lead II. Dog 8 kg. Slight nembutal narcosis.

during the standing position and might critically affect the heart as seen in the myocardial damage of the dog due to aconite.

### CONCLUSIONS AND CLINICAL SIGNIFICANCE

First, it should be emphasized again that in healthy persons of both asthenic and pyknic builds, alterations in the electrocardiogram, especially in the final deflection, take place during period I in the standing position. But in healthy persons such changes disappear in period E. This point seems to have been overlooked by some workers.<sup>15</sup>

In contrast, many cardiac patients show pathologic electrocardiographic changes in period I and further in period E in the upright position. In one group of patients who did not show any pathologic electrocardiogram in the recumbent position, pathologic changes appeared in the final deflection in period I on standing and did not disappear in period E.

Similarly, pathological electrocardiographic changes in persons with myocardial defects or coronary disease were aggravated in period E during standing position. Such alterations (depressions of S-T segments and isoelectric or inverted T-waves) were observed in Lead I or II and in the chest leads.

The clinical observations and the results of animal experiments suggest that deficiencies in the function of the heart (due to myocardial or coronary disease) might be revealed in a simple manner by the method described.

This test can be carried out without imposing a burden on the heart of a patient. On the other hand, some accidents have been reported which occurred during exercise test and during anoxemia tests.<sup>4, 11, 18</sup> (Just recently there appeared two reports of fatal accidents during the exercise test.<sup>9, 13</sup>)

Moreover, some insight into the nature of heart block can be obtained by electrocardiographic records in different positions.<sup>16</sup>

It seems that the described method might be of some prognostic value. The electrocardiographic alterations observed during standing in patients with myocardial disease vanished quickly on resumed recumbency if the disease was mild, but slowly if the disease was more severe.

It might be added that in some conditions of postural hypotension and in neurocirculatory asthenia, similar electrocardiographic changes might be observed in the standing position. However, these conditions are accompanied by other symptoms (i.e., fainting, dizziness, etc.) so differential diagnosis can be made easily.

The author wishes to thank Miss M. E. Laslo for her technical assistance.

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# HYPERTENSION AS A REACTION PATTERN TO STRESS; SUMMARY OF EXPERIMENTAL DATA ON VARIATIONS IN BLOOD PRESSURE AND RENAL BLOOD FLOW\*

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THERE has long been an awareness of a relationship between life situations, emotions and the level of blood pressure in normal and hypertensive subjects. Moreover, it has been suspected that such pressor effects have relevance to the pathogenesis of essential hypertension but the connection has not been established. The present investigation was undertaken in an attempt to explore this possibility.

Thus far investigations of this relationship have proceeded chiefly along one of two lines. O'Hare in 1920 demonstrated experimentally among hypertensive subjects significant pressor responses during what he called "excitement" induced, for example, by a discussion of members of the subject's family.<sup>1</sup> He provided no data concerning the personalities of the subjects or the nature of the conflicts involved. On the other hand, Moschowitz<sup>40</sup> had already observed that extreme cautiousness, paucity of fantasy life and inability to "enjoy themselves" were traits characteristic of hypertensive patients. Further and more detailed personality studies of subjects with essential hypertension have been accomplished by Alexander,<sup>2</sup> Saul<sup>3</sup> and Binger et al.<sup>4</sup>

Attempts to induce hypertension experimentally in animals have led to the emergence of two theories of pathogenesis: "neurogenic" and "humoral." It is becoming increasingly likely from the accumulating data that both mechanisms are operative in a synergistic way in essential hypertension.<sup>5</sup> In this regard the recent report of pyopagus twins with communicating blood vascular systems is significant. One had a relatively sustained hypertension and the other a labile blood pressure which occasionally rose to hypertensive levels.<sup>41</sup> Through Goldblatt's work<sup>6</sup> interest has become focused on the circulation of the kidney and on humoral products of renal ischemia. Recently a vasoexcitor material has been identified by Shorr<sup>7</sup> and his co-workers in dogs with temporarily impaired renal blood flow from shock. This material they found also in the blood of human subjects with essential hypertension.<sup>8</sup> The method of measuring renal blood flow in the intact human subject developed by Homer Smith<sup>9</sup> and his associates has allowed of a study of the relationship of emotional reaction, blood pressure and renal blood flow in man.

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Smith<sup>9</sup> demonstrated in man during sudden fright a pressor effect associated with reduced renal blood flow similar to that induced by injection of epinephrin. Visscher, in animals, has shown that stimulation of the sympathetic nerves to the kidney is likewise followed by blood pressure elevation.<sup>10</sup> Shorr and his co-workers have noted among hypertensive dogs sharp rises in the concentration of vasoexcitor material when samples of blood are drawn by unfamiliar workers or under other circumstances of stress.<sup>11</sup> Recently Ferris<sup>12</sup> has added new data to this accumulating body of evidence that either or both neural and humoral mechanisms may be involved during stress and in association with emotional conflict. He found, by blocking sympathetic impulses with tetraethyl ammonium bromide (T.E.A.), that the ultimate level of blood pressure (T.E.A. floor) varied with the state of relaxation and security of the subject. While it was high during periods of anxiety it was found at lower levels during relative serenity. The difference in blood pressure level after neural block with T.E.A. he attributed to the activity of circulating humoral agents.

Whatever the inferences which can be drawn concerning the pathogenesis of essential hypertension, it is clear that the distribution of circulating blood in the hypertensive is vastly altered. He has less blood flowing through the kidneys and other splanchnic areas, less through the skin and more through the skeletal muscles than do non-hypertensive subjects.<sup>13, 14</sup> As Cannon has pointed out, the cornered man or animal whose arterial pressure is elevated is mobilized for fight or flight.<sup>15</sup>

## METHOD

Fifty-eight hypertensive subjects who had a resting-seated diastolic blood pressure repeatedly and consistently 100 or higher were picked at random from the patients of the New York Hospital. None gave evidence of vascular anomaly or primary renal disease from urinalysis, pyelograms, urea clearance and concentration tests. They were considered to have "essential hypertension." This group was compared to 42 non-hypertensive healthy individuals and 150 subjects with vasomotor rhinitis and bronchial asthma. The clinical course of the subjects was closely followed over a period of one to three years and at the same time their personalities, attitudes, habits and general behavior were studied in detail under a variety of circumstances.

Twenty-one of the 58 hypertensive subjects were subjected one or more times to measurements of renal blood flow. Fifteen of the normal subjects were similarly studied. The procedure followed was essentially that outlined by Goldring and Chasis.<sup>10</sup> Sodium para-amino hippurate was utilized for measurement of effective plasma flow. Inulin, determined chemically by a modification of a method described by Hubbard and Loomis,<sup>17</sup> and mannitol, determined by the method of Corcoran, Lowenstein and Page<sup>18</sup> were utilized for the measurement of glomerular filtration rate. The subjects were all adequately hydrated prior to the experiment and urine was collected by

catheter. The total time of the experiment varied from 120 to 150 minutes and was divided into collection periods lasting 15 to 20 minutes each.

After two or three control periods during which the subjects were lightly entertained and diverted and the environment was maintained as neutral as possible, topics involving significant personal conflict were abruptly introduced into the conversation. This discussion was then carried on for two periods lasting 30 or 40 minutes. At the end of this time the subjects were strongly reassured and attempts to promote relaxation and diversion were undertaken for the remaining periods of the experiment.

Six of the hypertensive subjects were thus examined before and at varying intervals after lumbodorsal sympathectomy.

### OBSERVATIONS

*A. Relation of blood pressure level to attitude, emotions and life situation.* Variations in the course of hypertension are very difficult to evaluate because usually symptoms bear little relation to the height of the blood pressure. Frequent sphygmomanometric determinations of blood pressure, however, showed major variations from time to time in the subjects followed. The variations corresponded fairly clearly with changes in the general level of security of the individual. Examples are shown graphically in figures 1 and 2.

The patient whose findings are shown in figure 1 was a 48 year old civil service employee who was discovered to have hypertension (175 mm. Hg systolic and 125 mm. diastolic) in January, 1946 when he came to the hospital complaining of a recent left facial palsy. The latter cleared up uneventfully over a period of weeks, but his hypertension persisted. Figure 1 shows the recorded variations in his blood pressure over a period of nearly two years. His mother, a strong, domineering individual, has hypertension. She expected perfect behavior of the patient, and she allowed his older brother to "boss" him. At 36, against his mother's wishes, he was married secretly to a 34 year old schoolteacher. His wife was also strict and exacting. "She doesn't believe anyone has any nerves." For the first year he continued to live at home supporting his mother rather than his wife. Finally, they set up a menage of their own, but he was never able completely to emancipate himself from his mother. His Bell's palsy and the discovery of his hypertension occurred shortly after a serious conflict between his wife and mother. After he consulted the clinic it was repeatedly demonstrated that his blood pressure fell to lower levels when he was able vigorously to ventilate his resentments against his wife. He was particularly humiliated by her failure to disclose the amount of her earnings as a schoolteacher. Finally, she was interviewed and her coöperation enlisted in an attempt to build up his confidence and support him in a frustrating situation at work where he felt that he was being discriminated against because of his affiliation

with the minority political party. Following the enlistment of his wife's support a normal blood pressure was recorded on March 4 (figure 1). He said that he had been able to "talk back to the boss and get my own way. When I see the big boss now he smiles. It seems that after each fight he smiles more. Maybe he's beginning to realize I'm not a pushover. Since I have been coming here they treat me better down at work." His blood pressure was high again, however, six weeks later following what he considered to be an arduous experience of being presented at conference and having to reveal his brother's much more favorable status, both financially and in his mother's eyes. A week later his pressure was again low in a setting of satisfaction over optimal relations with his wife. By July, 1947 the conflict between his

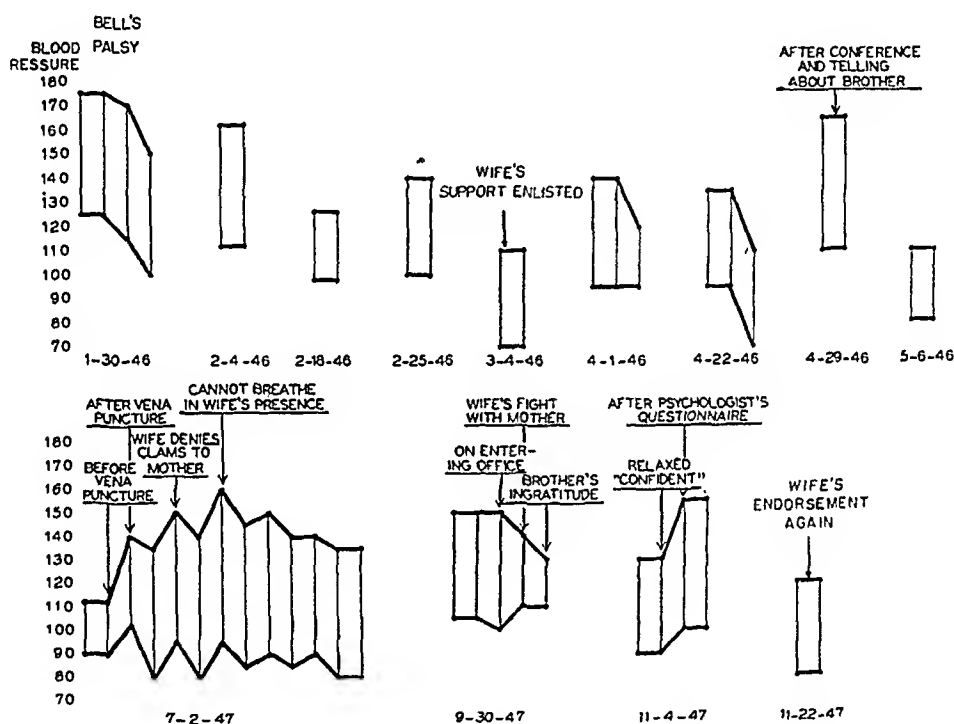


FIG. 1. Variations in level of blood pressure over a period of two years in a 48 year old civil servant. Note close correspondence of changes to status of relations with wife.

wife and mother had again become troublesome. The patient was particularly disturbed because his wife, in distributing some clams which he and she had collected, refused to give any to his mother. Even the discussion of this topic was associated with a brisk elevation of blood pressure. The problem was again dealt with as before, and finally when he felt "on top of the situation" again by November, 1947 his blood pressure was within normal range.

In figure 2 is illustrated the case of a 41 year old essentially asymptomatic hypertensive whose blood pressure elevation was also accidentally discovered at a time when he appeared for examination for promotion to public school

principal. His conflicts centered particularly about his wife who considered him socially inferior and a poor provider. Even when his blood pressure was at normal levels it could be made to rise repeatedly by a discussion of his wife (figure 2). The blood pressure could be made to fall, on the other hand, during a discussion of his vacation. He was eager to secure a Ph.D. degree in psychology and had been working on a thesis without much interest or support from his wife. She considered it a waste of time because it was not lucrative. He finally acceded to his wife's wishes and undertook a remunerative but what he considered undignified job as salesman for a toy balloon company. His blood pressure was then recorded at high levels (see October 13, 1947 in figure 2). Later, November 26, 1947, when he was busily engaged on the thesis, his blood pressure was within the normal range, but it rose again when he was in conflict about an extra-marital love affair.

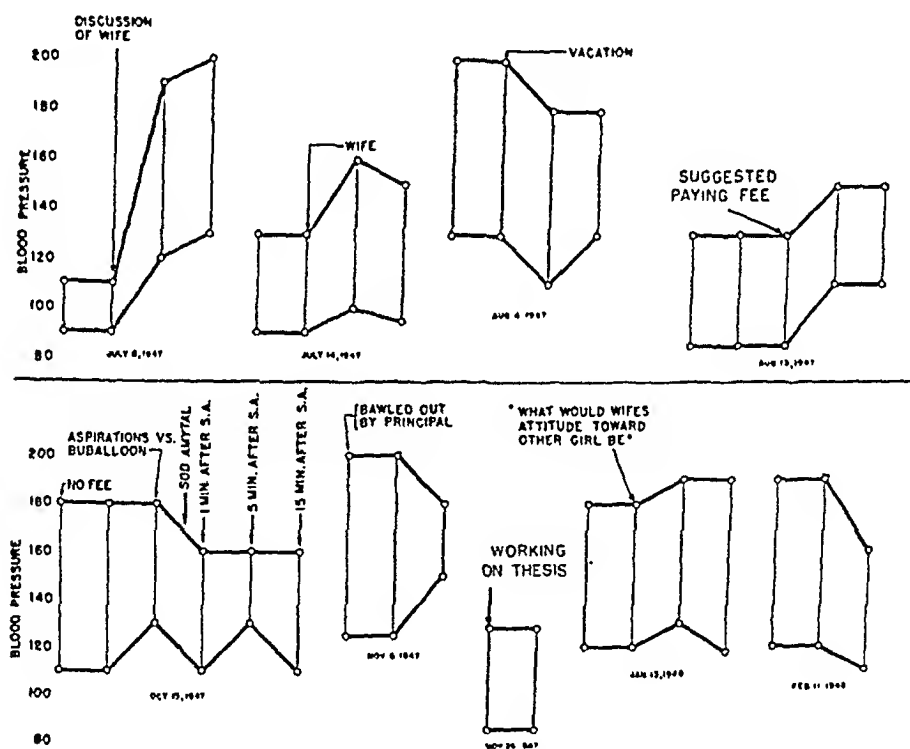


FIG. 2. Variations in level of blood pressure over one and one-half years in a 41 year old public school assistant principal. Note relatively little effect of sodium amytal administered at a time of serious fundamental conflict.

*Comment:* It is appreciated that inferences concerning the usual level of blood pressure cannot be drawn from single sphygmomanometric determinations even if they are made at frequent intervals, even daily, because of the rapidity with which variations occur and the fact that the person taking the blood pressure may enter into the equation. The findings do, however, support the belief that the subject's attitudes and feelings have a good deal to do with the level and that under maximally favorable circumstances the blood pressure may be within normal limits.

A 25 year old Armenian factory worker, for example, invariably had elevated blood pressure when the determination was made by his regular physician, a kindly but rather stern and quick moving individual. Even after intravenous injections of sodium amytal with strong reassurance his arterial pressure remained high as shown in figure 3. When, on the other hand, another physician whom he considered more sympathetic took the blood pressure it was repeatedly and consistently much lower (figure 3).

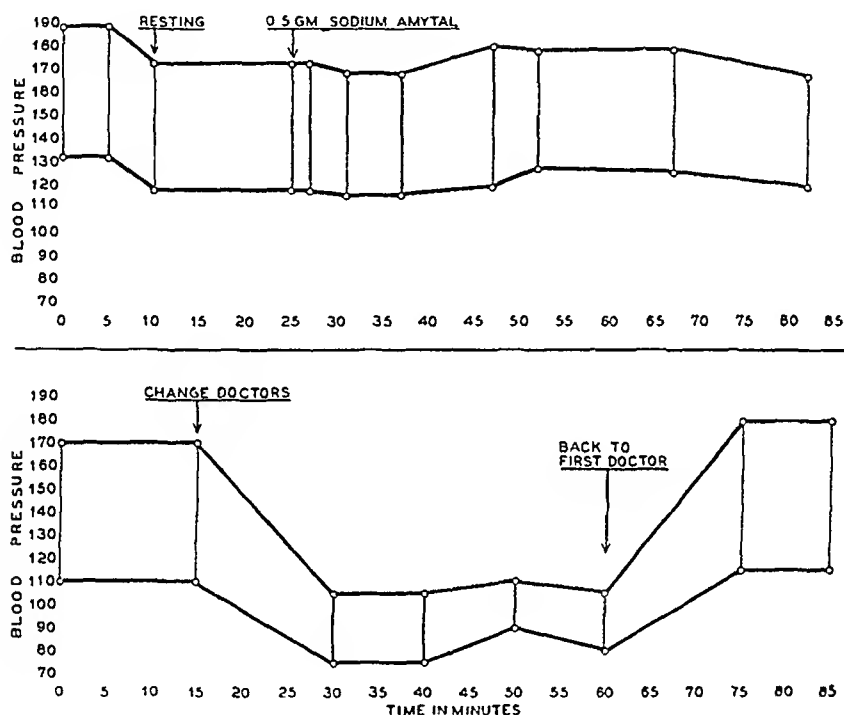


FIG. 3. Failure of intravenously administered sodium amytal to lower blood pressure while a temporary shift of physicians effected a profound lowering without drugs.

In a few subjects inferences could indeed be drawn concerning blood pressure level even from occasional determinations because there existed a 1 to 1 relationship between some symptom and elevation of blood pressure.

Thus, a 53 year old fur cutter complained of attacks of "lightheadedness" for five months prior to his first visit to the hospital. He was found to have hypertension (160 mm. Hg systolic and 100 mm. diastolic). In figure 4 are shown the variations in blood pressure recorded in this subject over a period of two years. The correlation of high readings with dizziness is clear, and hence the presence or absence of dizziness in this patient probably allows of inferences concerning the relative height of the blood pressure. His attacks were found to correlate closely with his attitudes and general feeling of security.

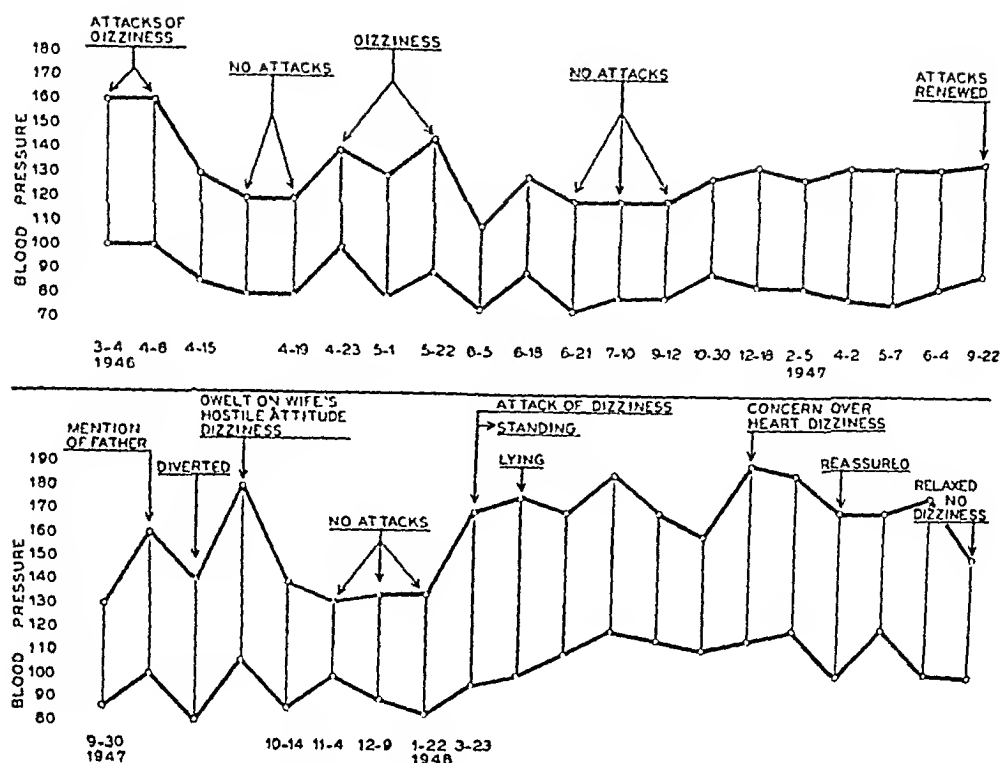


FIG. 4. Correlation of level of arterial pressure with the occurrence of attacks of "dizziness" in a 53 year old man.

*B. Measurements of renal hemodynamics.* Among the 21 hypertensive subjects who underwent measurement of renal blood flow it was invariably possible, by introducing topics which aroused serious conflict, to bring about a sharp rise in both systolic and diastolic pressures. These were more or less sustained throughout the period of the traumatic interview. The technical manipulations involved in the test and idle conversation, however, were not effective in raising the blood pressure.

The character of disturbance in the subjects was not one of sudden fright or alarm as in the case of Smith's subjects.<sup>9</sup> On the contrary, they usually appeared quiet and restrained without sweating and tremor and displayed none of the usual evidences of "nervousness." Despite their restraint and outward calm, however, they commonly asserted that they had felt anxious, frustrated or resentful during the interview. The findings in four of these subjects are shown in figure 5. They constitute a reliable sample of the whole group. It will be noted that during the control period renal blood flow was near the lower level of what is considered to be "normal." A prompt decrease in blood flow occurred coincident with the rise in arterial pressure during the interview and the diminution of renal blood flow usually outlasted the period of elevated blood pressure. The glomerular filtration rate varied only slightly but the filtration fraction rose.

When the resistance offered by the renal vasculature during the period of rise in blood pressure was determined by calculating the ratio of the mean

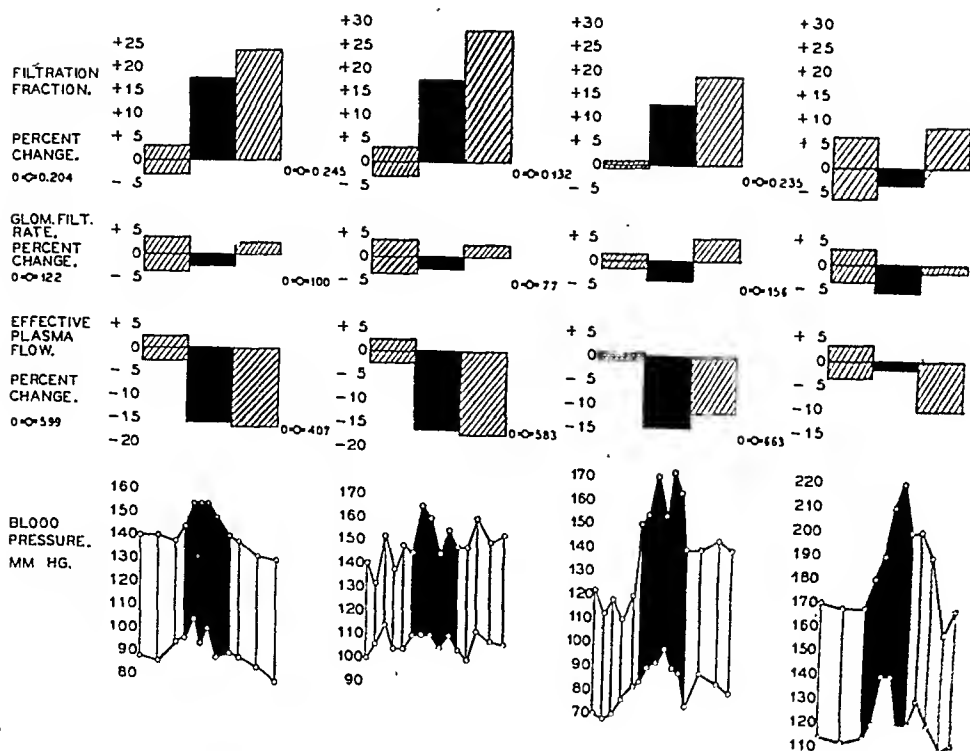


FIG. 5. Changes in blood pressure and renal hemodynamics in four representative subjects of the 21 tested.

The first section of cross-hatching represents the range of variation of three separate control periods. The mean value in each instance is shown at the left of the scale as ⊗. The solid black column represents the average change during the periods of traumatic interview and the last cross-hatched column shows the average change in the post-interview periods.

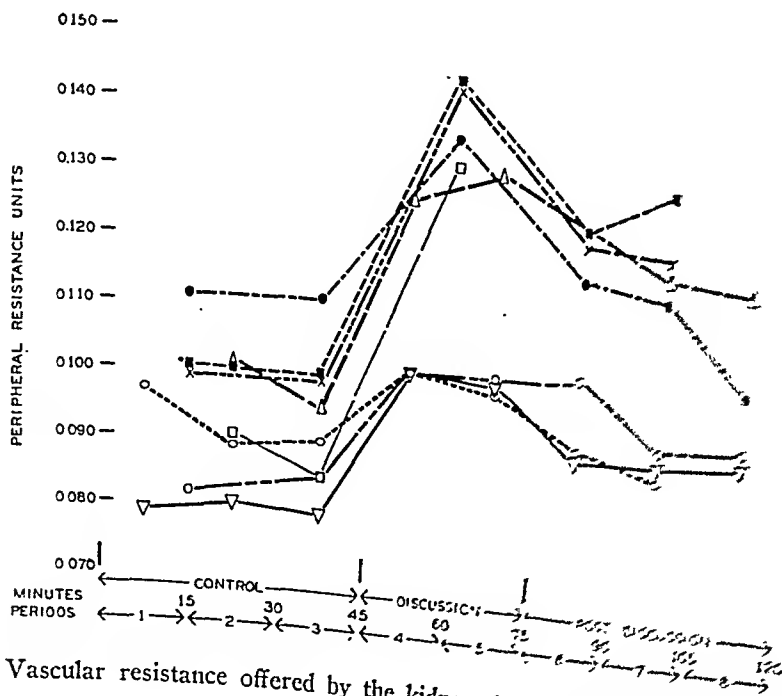


FIG. 6. Vascular resistance offered by the kidneys before, during and after interview.



blood pressure to effective renal blood flow, as high as a 45 per cent increase in resistance to blood flow was observed (figure 6). Usually the renal vasoconstrictor effects considerably outlasted the period of elevated blood pressure.

Of the normal subjects thus studied, nine displayed a moderate rise in both systolic and diastolic arterial pressures during the discussion of conflicts. With the elevation of arterial pressures there also occurred evidence of slight renal vasoconstriction. Four of the normal subjects showed no significant change in blood pressure and in the case of one subject the blood pressure decreased slightly without evidence of change in renal hemodynamics.

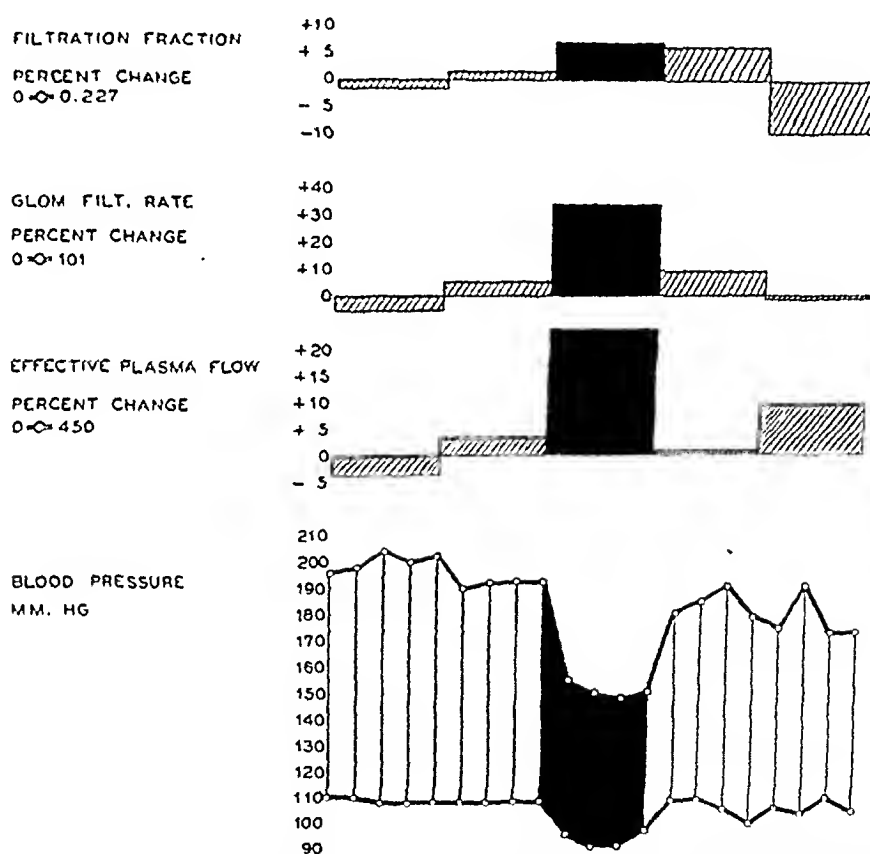


FIG. 7. Abrupt fall in arterial pressure associated with increased renal blood flow following intravenous injection of sodium amytal. Solid black column designates the values obtained during the collection period immediately after intravenous injection of sodium amytal.

In one hypertensive individual the procedure was varied in an attempt to induce a lowering of blood pressure so that its effect on renal hemodynamics could be assessed. Accordingly, a 53 year old man was given 0.5 gm. sodium amytal intravenously during a period of anxiety and relatively high arterial pressure. The injection was accompanied by strong reassurance. A considerable decrease in blood pressure was effected and with it there was observed an increase in renal blood flow and glomerular filtration. After 15

minutes of reassurance and low blood pressure, a topic of significant conflict was touched upon. Promptly the blood pressure rose to its former level and the renal blood flow and glomerular filtration rate diminished (figure 7).

*Comment:* Among the subjects whose renal hemodynamics were measured, the filtration fraction was always elevated when there occurred a decrease in renal blood flow. According to Smith<sup>19</sup> this indicated an increase in the efferent arteriolar resistance. The application of the formulae of Lamport,<sup>20-23</sup> however, yielded evidence of a constriction of afferent arterioles as well.

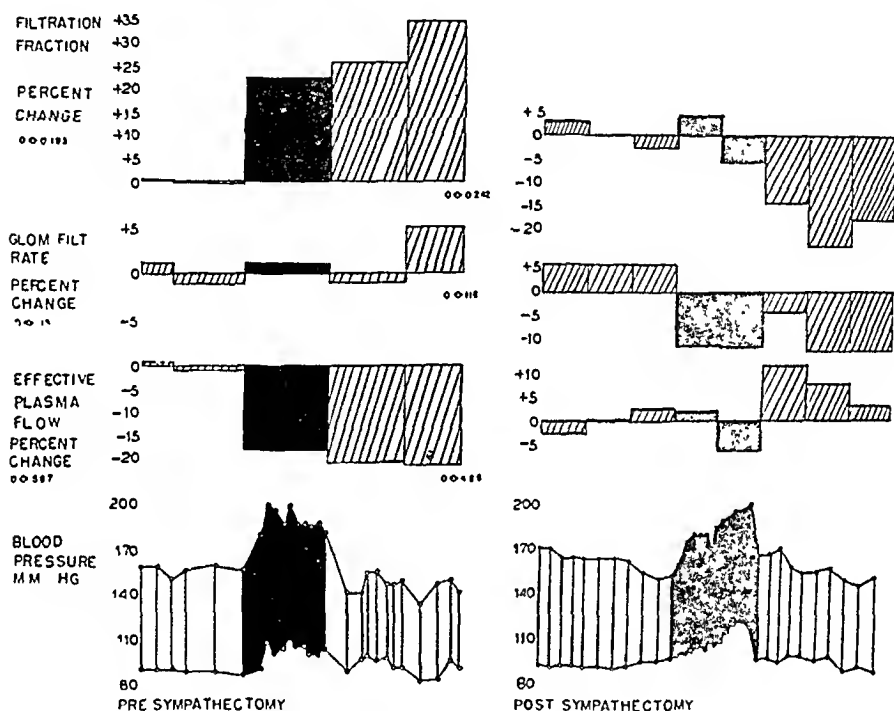


FIG. 8. Modifiability of blood pressure and renal hemodynamics by traumatic interview pre- and post-sympathectomy (Smithwich thoraco-lumbar procedure).

Because epinephrin also induces a fall in plasma flow and rise in filtration fraction, it has been proposed that the efferent arteriole was subject to the control of the adreno-sympathetic system. In favor of this inference is the observation of Richards and Plant<sup>24</sup> and Winton<sup>25</sup> of expansion of the kidney with fall in renal blood flow noted during direct observation of the kidney following minute doses of epinephrin. Livingston observed the same effect after weak stimulation of the splanchnics.<sup>26</sup> Against this interpretation is the fact that sympathectomy and high spinal anesthesia in humans fail to cause significant changes in renal blood flow<sup>10, 27, 28, 29, 30</sup> and similar observations in the case of the autotransplanted kidney in the dog.<sup>31</sup> It is conceivable that since all these studies were done in the basal or "standard" state the failure to observe changes in renal blood flow might be attributable

to relatively minimal sympathetic activity during periods of rest. Therefore, special note of these relationships was made in the six hypertensive subjects who were restudied in the experimental interview situation at varying intervals following sympathectomy.

*C. Effects of sympathectomy.* The prototype of the results observed among the six sympathectomized subjects is shown in figure 8 where the pre-sympathectomy findings are contrasted with those post-sympathectomy. It is evident that although after sympathectomy the blood pressure rose during the traumatic interview just as readily as it did before, the accompanying renal vasoconstriction no longer occurred and there was no rise in filtration fraction. The peripheral resistance in the kidney as calculated by the ratio mentioned above no longer rose so high and the component attributable to efferent arteriolar constriction was lost.

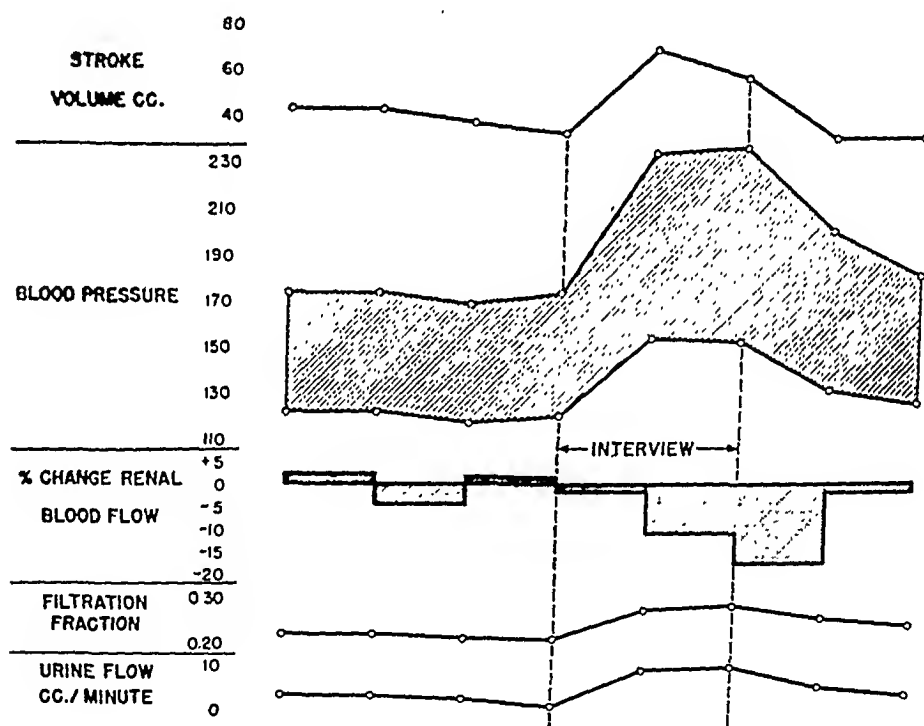


FIG. 9. Increased cardiac output associated with elevation of blood pressure and renal vasoconstriction during traumatic interview.

*D. Simultaneous measurement of cardiac output.* In two subjects, reported elsewhere in detail,<sup>32</sup> the determinations of renal hemodynamics were made while they were reclining on a Nickerson ballistocardiograph, critically damped and connected to a direct writing recorder.<sup>33</sup> In both instances during the traumatic interview the blood pressure rose briskly and at the same time there was recorded a significant increase in stroke volume as well as heart rate and hence in cardiac output (figure 9).

One of these subjects was retested in this fashion after sympathectomy. During the interview her cardiac output increased as it had before operation

and the renal findings were similar to those of our other sympathectomized subjects described above.

*Comment:* The inferences which can be drawn from these data are: (1) It is possible at will to invoke in hypertensive subjects an accentuation of their characteristic biologic pattern of mobilization by confronting them with an adequate threat to their security. (2) This reaction includes a sharply decreased supply of blood to the kidneys. The blood flow is obviously shunted elsewhere since the cardiac output may be increased and the pressure in the system is higher. (3) The renal vasoconstriction involves both the afferent and efferent arterioles. (4) This process may be temporarily reversed by appropriate measures which lower the blood pressure. (5) After bilateral lumbodorsal sympathectomy the general mobilization response in reaction to threats is modified but not abolished. It is still possible to elevate the blood pressure but the shunting of blood from the renal bed to such a degree no longer occurs. The renal vasoconstrictor effect which is lost after sympathectomy is predominantly that involving the efferent arteriole. The afferent arteriole may be governed by an intrinsic or humoral mechanism. These data reinforce the conclusions of Ferris referred to earlier, in which he identified a persistent humoral factor which induced elevation of blood pressure in response to situational threats following the elimination of neural effects.

Concerning the pathogenesis of this mobilization response, the older concepts of sympathicotonia and organ inferiority are inadequate because among hypertensives the blood pressure does not necessarily rise in response to stress. Under appropriate circumstances it may even fall. The direction of change appeared to depend rather on what the particular stimulus meant to the subject. When a reaction of mobilization was not evoked and the subject on the other hand felt defeated or overwhelmed a depressor reaction occurred.

*E. Nature of pressor stimulus—variability of cold pressor effect.* A striking example of this phenomenon reported in detail by Stevenson and Duncan<sup>32</sup> was encountered when a cold pressor test was administered to a pregnant hypertensive at a time when she was hyperreactive to noxious stimuli of all sorts, felt overwhelmed and unable to bear the pain involved. Accompanying the pain she experienced nausea, sweating and the blood pressure fell abruptly. A few minutes earlier a brisk pressor response had been elicited by a discussion of her forthcoming delivery, an event which to her was fraught with mixed feelings of guilt, frustration and resentment (figure 10).

Examples of variability in the degree and type of cold pressor response were frequently encountered. Again the significance of the event appeared to influence its effect upon arterial pressure. For example, when one man, a 28 year old steam fitter, thought that the decision as to whether or not he would undergo a mutilating sympathectomy hinged upon the outcome of a

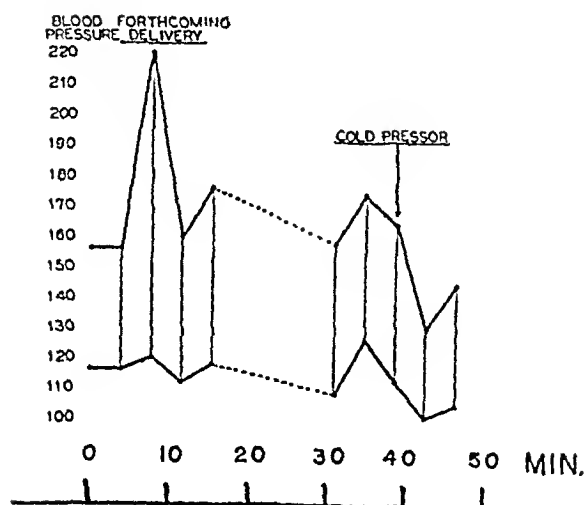


FIG. 10. Brisk rise in blood pressure in a hypertensive subject associated with conflict and resentment during discussion of forthcoming parturition. Precipitate fall when hand was plunged into ice water in a period of dejection, exhaustion and feelings of being overwhelmed.

cold pressor test, he displayed the response of a "hyperreactor." Later the same day, when he was reassured that the operation was not considered necessary, his blood pressure was lower initially and the test produced a "hyporeactive" response. Even at times when his initial pressure was high, however, his response was "hyporeactive" when the performance of the test had no special significance for him (figure 11).

The phenomenon of hypertensive reactions under one set of circumstances and hypotensive under another has also been recognized during the day-to-day follow-up of the clinical course of patients. This is exemplified by the

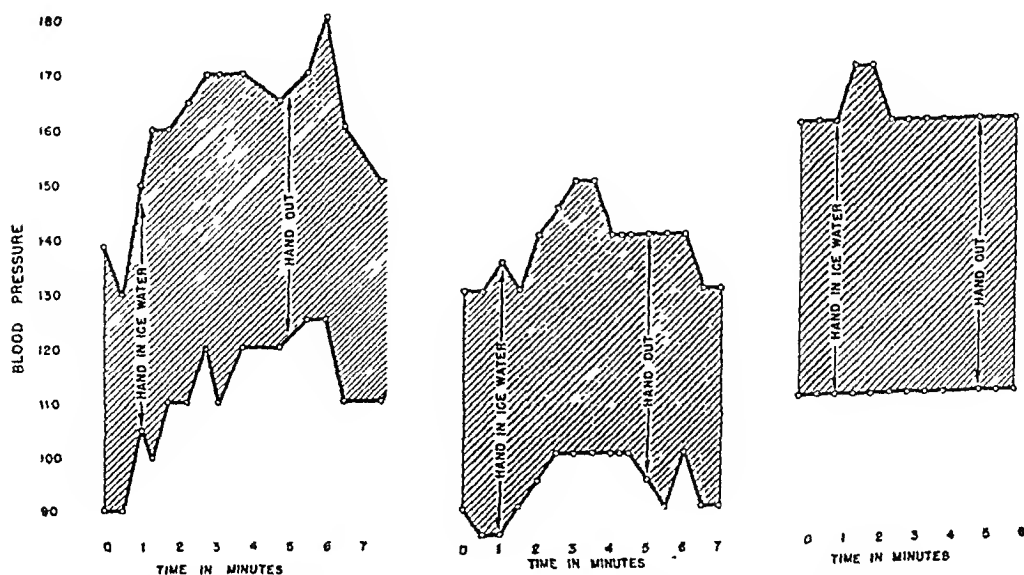


FIG. 11. Variations in cold pressor response in a single patient. The first two tests were done on the same day and the third a few weeks later.

case of a 48 year old married Jewess whose chief conflicts concerned the unsalutary relationship between her husband and older son. The former had not wanted children and considered the patient's open adulation for and extremely protective attitude toward their son a direct threat to his security. Consequently he punished the boy at every opportunity. The patient's hypertension was discovered at the time when her son was drafted into the Army. It persisted during the subsequent period until the news came that the boy was to be sent overseas. She felt overwhelmed and defeated by this prospect and continued dejected with much lower blood pressure until her resentment was again aroused by conflict between her husband and son and with that her blood pressure rose again to hypertensive levels. Later, at a time when the patient was catheterized, a procedure to which she reacted with overwhelming shame, she again displayed a precipitous transitory fall in blood pressure with sweating and tachycardia (figure 12). This observation has been repeated on three separate occasions with similar results each time.

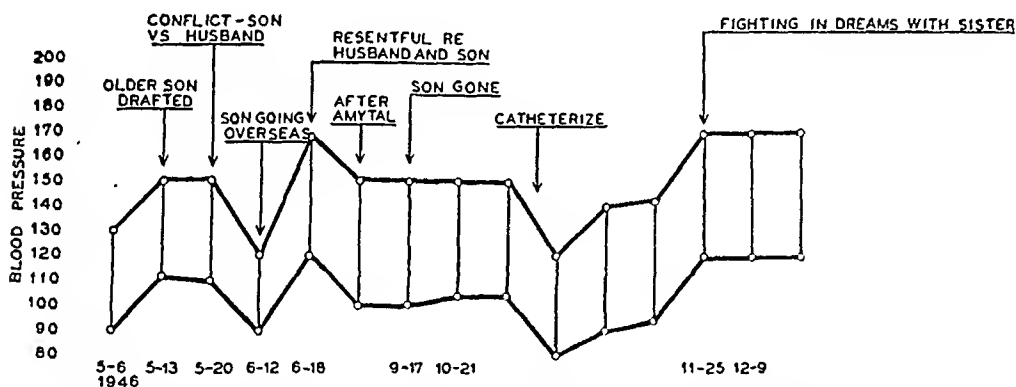


FIG. 12. Episodes of lowered blood pressure associated with feelings of defeat in response to overwhelming events occurring in a subject with essential hypertension who reacted to most stresses with more aggressive feelings and elevation of blood pressure.

*Comment:* Wolf and Wolff<sup>34</sup> and more recently Hickam, Cargill and Golden<sup>35</sup> have similarly shown that elevation of blood pressure constitutes a part of only one kind of cardiovascular response to situational threats, a hyperdynamic one. Under appropriate circumstances another subject or even the same individual may react with a hypodynamic response including a lowering of blood pressure. The latter was characteristically accompanied by feelings of defeat or dejection in contrast to the tense, aggressive attitude which accompanied hypertension.

*F. Personality features and reactions of persons with arterial hypertension.* Our personality study and diary of attitudes and behavior of these subjects substantiated in a striking way the concept that their hypertension represented an emergency mobilization pattern inappropriately used and unduly sustained. Fifty cases out of 58 on careful study generally fitted the following description. In agreement with the findings of Sheldon<sup>36</sup> they

were more square and muscular than average. They were non-reflective and displayed a taste for dealing with problems by action. Many of them exhibited signs and symptoms of excessive skeletal muscle tension. From the standpoint of attitudes as well as circulatory physiology they were mobilized for combat, but did not engage in it against the pertinent adversary. Under a façade which was often affable and easy going, they were tense, wary and suspicious, afraid of committing themselves. They were poised to strike, but withheld their punch with a guilty fear of its consequences. At the same time they displayed a strong need to conform and keep peace. This, coupled with inability to throw themselves wholeheartedly into things because of fear and suspicion, made it difficult for them to believe strongly in anything or to derive real satisfaction from their accomplishments. They felt a need to show prowess without exhibiting aggression and continually feared that they would not succeed in doing so.

Hypertensive individuals were found to take out their aggression in some vicarious way, by excelling in sports, or merely by an excess of general activity or excessive eating. They were prominently preoccupied with appearances and saving face. As children they were all unduly shy. They blushed easily and were rarely able to admit they were wrong. Most of the married ones selected domineering mates.

In the background of the subjects we studied were the following common circumstances which may have provided conditioning situations. Many of their mothers were stiff and domineering. They were inclined to demand compliance and withheld approval for failure to do so. They especially refused to tolerate outbursts of anger. Their children felt that they were forced to compete for affection and approval by being "good." Many of our hypertensives dealt fairly successfully with this challenge and managed for a time, at least, to consider him- or herself "closest" to the mother. This accomplishment inevitably involved the development of strong hostility toward the mother which was suppressed with varying degrees of success but was associated with guilt.

In brief, our hypertensive subjects, often gentle, poised and apparently easy going, were filled with aggressive drive which was tightly restrained by a need to please.

In order to bring into focus the characteristics of the hypertensive reaction pattern we compared them with a group of 150 subjects suffering from chronic vasomotor rhinitis or bronchial asthma reported in detail elsewhere.<sup>37, 38</sup> These latter in general were of a more linear build, less square and muscular and less hearty. They were found to display predominantly attitudes and behavior of defense and non-participation in contrast to the offensive aggressive but thoroughly bridled striving of the hypertensive. They were less preoccupied with pleasing but their attempt was to shut out rather than deal with the noxious environment.

Striking confirmation of this formulation of the general character structure and attitudes of the hypertensive implying his proclivity for meeting

challenges with a pattern of tightly reined mobilization is found in Friedman and Kasanin's study of apparently identical twins, one of whom was hypertensive.<sup>39</sup> They found that the non-hypertensive twin was the brighter and stronger of the two and the better in school. He was more relaxed and satisfied, expressed anger easily and recovered rapidly from humiliations. The hypertensive twin felt that he was at a competitive disadvantage with his brother, spent a great deal of time and energy trying to please people and had no enemies but suppressed resentment and hostility and carried them within him for a long time. He worked extremely hard and was "successful" but never felt much satisfaction in his day-to-day living.

Similar reaction patterns among hypertensives have been described by Binger and his associates,<sup>4</sup> by Alexander<sup>2</sup> and Saul.<sup>3</sup>

In several subjects an episode of lowered arterial tension followed a fairly uninhibited physical expression of aggression.

In figure 13 is illustrated an occurrence in a 36 year old purveyor of illicit merchandise who was able to cope with many "tight spots" but not with the contemptuous attitude toward the subject held by his brother-in-law with whom he was forced to live. After a particularly humiliating episode he came to the laboratory with a blood pressure of 165 mm. Hg systolic and 110 mm. diastolic. The results of his repressive pattern were pointed out and he was encouraged to deal with the problem another way. He went out and returned after "beating up" his brother-in-law. At that time his blood pressure was 125/85. He said that he felt relaxed and vindicated (figure 13).

To test further the relevance of situation to blood pressure our subjects were followed from week to week over a period of several years. They were

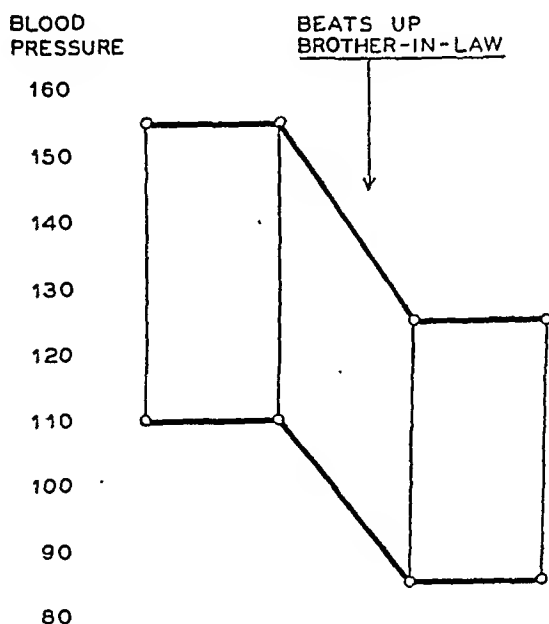


FIG. 13. Reduction of arterial pressure in an hypertensive subject following a fairly uninhibited physical expression of aggression.



given reassurance, encouragement, advice with their problems and opportunities to express their feeling and to discuss their interpersonal conflicts. An example of improvement under such management is provided by the case of a 28 year old steamfitter illustrated in figure 14. His principal conflicts related to his father who had forced him into the steamfitting business shortly before he deserted his wife and children. The patient, who really wanted to be a half time artist and half time prize fighter, was encouraged to sell his steamfitting tools. Following this his blood pressure remained relatively

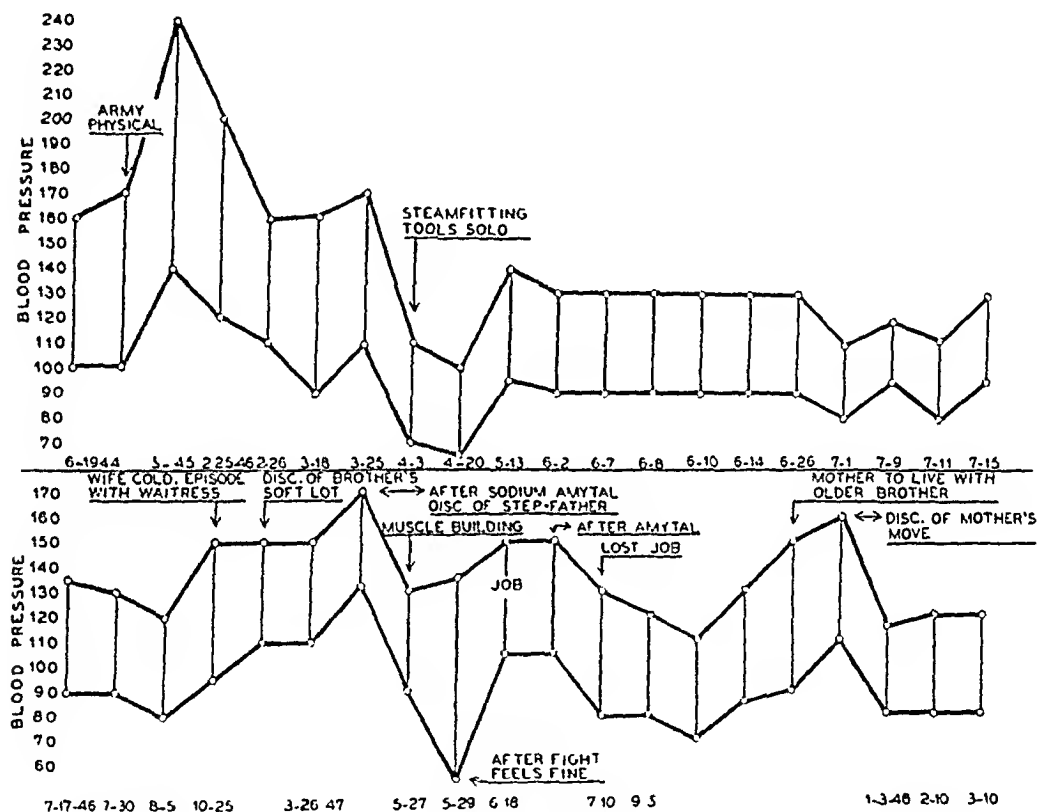


FIG. 14. Blood pressure variation over a period of four years in a 31 year old man.

normal for a period of months until he became involved in an extra-marital love affair. After this was terminated and he took out his excess energy in muscle building, his blood pressure fell again, only to rise when his wife tired of his meager earnings as a free-lance commercial artist and urged him back into the steamfitting business. Here, amytal failed to lower his blood pressure but it went down again after he arranged to lose his job. Another elevation occurred at a time when his mother, on whom he was very dependent, left him in New York and went to live in California with his brother. After strong reassurance and emotional support from the doctor his arterial pressure again fell and remained approximately normal for the next few months.

## DISCUSSION

The concept of bodily economy being maintained by an equilibrium of opposing forces acting on organs and organ systems commands wide interest and sympathy at present. It is also clear that the mass-action equations which are responsible for maintaining these equilibria are so highly sensitive that the reaction is caused to go predominantly in one or another direction by changes so minor that they cannot be detected by current sensitive methods of measurement.

Whether adaptive measures are automatic or voluntary is apparently unimportant as far as their relevance to the homeostatic mechanism is concerned. For example, the automatic thermoregulatory mechanisms such as increased muscle tension, shivering, or sweating are of the same order of phenomena as the voluntary ones, such as walking rapidly or putting on long underwear when the day is cold. They are all aimed at maintaining the homeostatic balance between heat production and heat loss.

The ducking which occurs when a missile is thrown at one's head may be automatic or voluntary but the distinction is unimportant. It is an appropriate defensive gesture to anticipate and ward off the adverse weighting of the equation which maintains homeostasis.

The tense, alert posture of sitting on the edge of the seat with which one anticipates a motorcar accident is a similar protective gesture but is far less appropriate. It would appear to have significance atavistically as a "readiness to spring," appropriate when dealing with danger which can be side-stepped or run away from but inappropriate and potentially costly when invoked in a motor car. A more satisfactory posture to assume in anticipation of an auto accident would be to relax completely and curl up on the floor of the car. By the same token elevation of blood pressure is an inappropriate way to meet the hazards of sibling rivalry or problems of marital adjustment. The difficulty would appear to consist in reserving the biologic pattern of mobilization for short term emergencies in which it is appropriate or at least not harmful, instead of adopting it as a way of life and applying it inappropriately to long standing threats from conflicts of interpersonal relations in job or family. Perhaps hypertension is an ancient protective reaction to preserve homeostasis, potentially useful to Man, especially in his early days, but certainly most costly and inappropriate when adopted as a sustained long term adaptive pattern.

Support for the point of view that such a pattern of reaction involves the cerebral cortex as well as lower neural structures derives from the work of Pool and his associates<sup>42</sup> who performed bilateral topectomy on two psychotic subjects with essential hypertension, removing the medial portion of Brodman areas 9 and 10. Prior to operation the blood pressure of the first subject ranged between 200 to 220 systolic and 120 to 130 diastolic. For two years since operation the average range has been 170 to 180 systolic and 100 diastolic. The continued moderate hypertension in this subject

suggests that part of the hypertensive mechanism at least may become irreversible to the interruption of cortical pathways. The second subject has only been followed for five months postoperatively but coincident with clinical improvement characterized by lessening of depression and decreased preoccupation with problems and conflicts, the blood pressure fell from an average range of 180 to 200 systolic and 110 to 120 diastolic to 120/80.

It has already been pointed out that the hypertensive subject differs in general from subjects with asthma in body build, personality structure, attitudes and behavior. Why a man, when his security system is seriously threatened, should develop hypertension instead of asthma, peptic ulcer or colitis, cannot be stated but it would appear that these disorders represent various possible patterns of reaction to threats. When a man's face is slapped by an adversary's glove he may choose pistols, sabres or boxing gloves, or he may elect to run away, to collapse at the feet of his challenger or sidestep the incident by retracting or making a joke of the incident. Why he chooses one course rather than another depends upon a myriad of factors including his inherited tendencies, his early experiences, his cultural background, his habits and skills, etc. The significant question for present consideration is the character of pattern which he does select and what its implications are for his health and survival. Hypertension is a costly protective device when utilized for more than short term emergencies. Adopted as a way of life it may lead to irreversible cardiovascular and renal damage and eventual death of the organism.

#### SUMMARY AND CONCLUSION

1. A group of 58 subjects with essential hypertension has been studied from the standpoint of overall reactivity to threats arising out of problems of day-to-day living.

2. It was found that they meet these threats and challenges with an attitude of restrained aggression and display a vascular reaction characterized by elevation in blood pressure and renal vasoconstriction.

3. Both the afferent and efferent glomerular arterioles participate in the constriction.

4. Following thoraco-lumbar sympathectomy the renal blood flow when the subject is at rest is unchanged. The arterial pressure continues to show elevation in response to situational threats, but the efferent glomerular arteriolar constriction during such rises is abolished. The constriction of the afferent arterioles persists.

5. The general attitudes, reaction patterns and behavior of hypertensives differ from those of subjects with bronchial asthma. In general the former are more offensive and the latter more nearly defensive in their dealings with life.

6. Hypertension may represent an atavistic protective reaction of mobilization, invoked inappropriately by these subjects to deal with day-to-

day stresses and threats arising out of problems of interpersonal relation. It becomes harmful and leads to illness when this essentially emergency pattern is adopted as a way of life.

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# AUREOMYCIN—A NEW ANTIBIOTIC: EVALUATION OF ITS EFFECTS IN TYPHOID FEVER, SEVERE SALMONELLA INFECTIONS AND IN A CASE OF COLON BACILLUS BACTEREMIA \*

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THERE has been a notable lack of success in the treatment of typhoid fever and salmonella infections with the chemotherapeutic and antibiotic agents that are now available. This has been true even with streptomycin which is usually quite effective against the causative organisms in vitro. Moreover, the failures of streptomycin in these infections and in some others like brucellosis have not usually been associated with the appearance of highly resistant variants as they are in most other infections, nor have they generally been associated with the presence of large and inaccessible areas of suppuration. Because these infections may be quite variable in their clinical course, it may be difficult to evaluate the effectiveness of any given agent without careful study of its use in cases of varying severity.

In this paper are presented the results of clinical and bacteriologic observations in a few cases of typhoid fever and salmonella infections and in a case of colon bacillus bacteremia that have been treated with a new antibiotic, aureomycin. Tests with this antibiotic in vitro and some observations in experimental infections in animals have suggested that this agent was effective against a large variety of gram-positive and gram-negative organisms including those of the typhoid-salmonella group and that it was also effective against infections with rickettsias and with viruses of the psittacosis-lymphogranuloma venereum group. This antibiotic therefore seemed worthy of a clinical trial to determine its field of usefulness in the treatment of human infections. A brief summary of the results of its use in 100 cases of various bacterial infections has been presented elsewhere.<sup>1</sup> Because of their special interest, the findings in the present cases are reported here in somewhat greater detail.

Some of the details concerning the isolation of aureomycin, its pharmacologic properties and its activity against various bacteria in vitro and against experimental infections in animals with a variety of different bacteria, rickettsias and viruses have been presented by workers of the Lederle Laboratories Division, American Cyanamid

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Company at a Conference on Aureomycin sponsored by the New York Academy of Sciences, July 21, 1948. Reports of other laboratory investigations with this agent and of its clinical use were also made at this conference by several other groups of workers including the present authors.

Aureomycin was found to be highly stable in the form of a dry powder, and it also maintained its potency for at least two weeks when kept at high concentrations in distilled water at pH 4.0, either at incubator or ice box temperatures. It loses potency very rapidly, however, when kept at low concentrations in broth, serum or blood agar at 37° C. and somewhat less rapidly at 4° C.<sup>2</sup>

Bacteriologic observations in this laboratory<sup>2</sup> have indicated that aureomycin is active in vitro against many recently isolated pathogenic strains of bacteria including various cocci and gram-negative bacilli and also against penicillin resistant, streptomycin resistant and streptomycin dependent organisms. The number of organisms inoculated and the pH of media greatly influence the antibacterial action of aureomycin and it is effective only against actively multiplying organisms. There is no marked tendency for organisms to become resistant to aureomycin after single or repeated exposures of large numbers of bacteria or during treatment of patients with this agent. A moderate increase in resistance, however, was attained in some strains by repeated subculture in the presence of increasing concentrations of the antibiotic.

In human subjects aureomycin activity appears quite rapidly in the urine after its oral administration, and concentrations of 64 to 256  $\mu$  g. per ml. may be demonstrated in urine collected between two and 16 hours after a single dose of 0.5 or 0.75 gram in adults. The greatest rate of excretion after such doses occurs between two and eight hours. Some aureomycin activity could still be demonstrated in the urine for as long as 72 hours after a single dose or after the last of a series of oral doses. The maximum values for plasma concentrations of aureomycin after single or multiple oral doses of 0.5 or 1.0 gram were usually found to be about 2  $\mu$  g. per ml. or less but the methods used for these determinations were not entirely satisfactory.<sup>3, 4</sup>

Clinically aureomycin appears to be effective when given by mouth and is relatively nontoxic.<sup>1</sup> Intramuscular doses of the hydrochloride dissolved in distilled water are very irritating due to the high acidity of the substance but the irritation may be overcome somewhat by the use of proper buffers and/or by the incorporation of procaine with each injection. Favorable results were reported, at the conference mentioned, in early clinical trials in cases of lymphogranuloma venereum,<sup>5, 6</sup> granuloma inguinale,<sup>5</sup> various types of infections of the eye,<sup>7</sup> gonorrhea,<sup>1</sup> pneumonia,<sup>8</sup> meningococcemia,<sup>8</sup> nonspecific urethritis,<sup>1</sup> brucellosis,<sup>9</sup> typhoid fever<sup>1</sup> and some urinary tract infections.<sup>1, 4, 9</sup> The results in the treatment of various rickettsial infections<sup>1, 10</sup> were most encouraging.

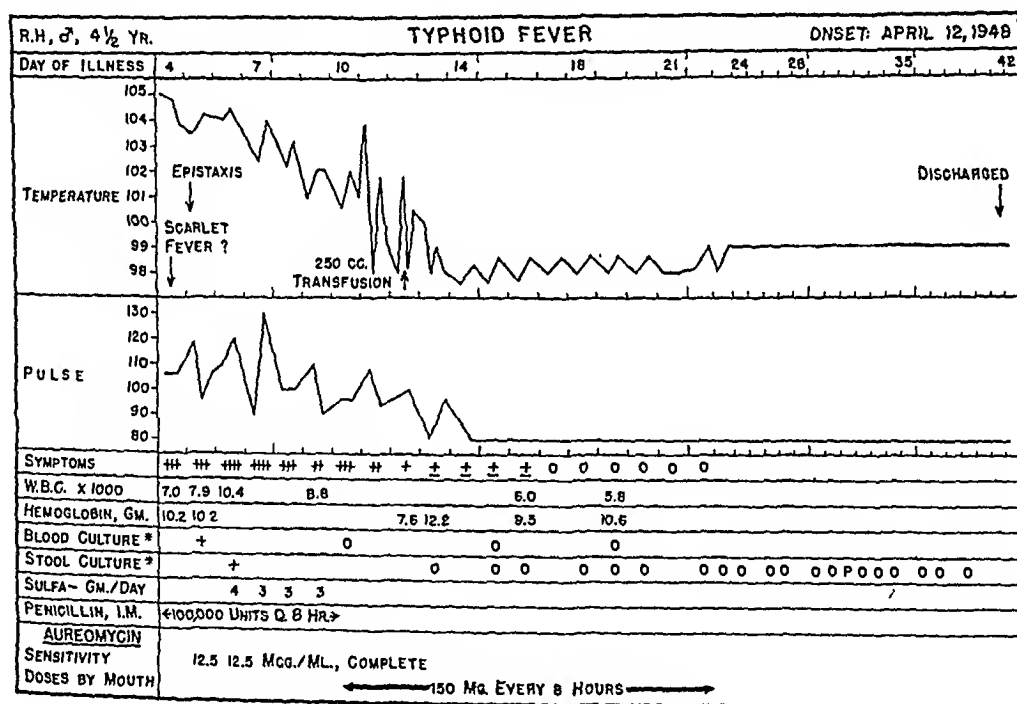
#### PATIENTS, MATERIALS AND METHODS

The patients selected for this study were admitted to the Boston City Hospital in the spring of 1948. They varied in age from 14 months to 80 years. Except for the typhoid carrier, they were all acutely ill and the causative organism was obtained from their blood and/or stools before treatment was begun. All of the aureomycin was given by mouth except in two patients who received small doses intramuscularly in addition. Since these patients were among the first to receive oral therapy and the toxicity of the compound in humans was not known, the doses used at first were considerably smaller than those which subsequent experience has shown to be feasible and perhaps necessary.

Specimens of blood, stools and urine were obtained before, during and after treatment with aureomycin whenever indicated and feasible. The isolation and identification of the organisms were carried out by Marion E. Lamb and A. Kathleen

## CASE REPORTS

The significant clinical and bacteriologic data in the various patients are shown in figures 1 to 9 and in table 1. Only a few brief comments will be made concerning the features of special interest in each of these patients. The case of the typhoid carrier is of particular interest and will be considered separately.



\* += S. TYPHOSA; P= OVERGROWN BY PROTEUS; O= NEGATIVE FOR S. TYPHOSA.

FIG. 1.

*Typhoid Fever.* Five of the patients were treated for typhoid fever. The first of these patients, R. H. (figure 1), was first seen at the South Department on the tenth day of illness after he had apparently failed to respond to treatment with penicillin and sulfadiazine, although his temperature and pulse rate appeared to be on the down grade at the time. Clinical improvement in this patient was quite rapid after aureomycin treatment was started and typhoid organisms could not be obtained from cultures of his blood or stools thereafter, although they had previously been obtained on one occasion



Summary of Relevant Clinical and Laboratory Findings in Cases of Typhoid Fever, Salmonella Infections and Colon Bacillus Bacteremia Treated with Aureomycin

Patient	Sex	Age, Yrs.	Diagnosis, Organism	Sensitivity, Complete µg./ml.	Clinical Findings before Aureomycin Therapy					Aureomycin Therapy			
					Severity	Fever	Symptoms	Previous Chemotherapy		Day of Disease		Dosage (oral, except when noted)	Total, Gm.
								Drug	Days	Begun	Ended		
R. H.	M	4½	Typhoid fever, <i>S. typhosa</i>	12.5	+++	105-102	Disoriented, vomiting, distended, diarrhea. Hemoglobin 10 gm.	Sulfaguanidine Sulfadiazine Penicillin	1 4 7	10	23	0.15 gm. every 8 hrs.	5.85
J. H. (sister of R. H.)	F	1½	Typhoid fever, <i>S. typhosa</i>	12.5	++	104-101	Vomiting and apathy. Had typhoid vaccine 2 days before onset	None		8	23	0.05 gm. every 8 hrs.; then every 6 hrs.	3.0
L. O'C.	F	2	Typhoid fever, <i>S. typhosa</i>	12.5	+++	100-105	Irritable, vomiting, diarrhea, anorexia	Penicillin	5	8	21	0.15 and 0.1 gm. alternately every 12 hrs.	3.4
M. O'C. (sister of L. O'C.)	F	3	Typhoid fever, <i>S. typhosa</i>	25	++	103	Anorexia, listless, diarrhea, distended. Hemoglobin 75%	None		5	26	0.1 gm. every 6 hrs.	8.4
A. L.	M	60	Typhoid fever, <i>S. typhosa</i>	6.3	++++	101-102.4	Remission of fever 12 to 18 days after onset, then acutely ill with headache, diarrhea, sweating and prostration. Hemoglobin 9 gm.	None		22	44	0.5 gm. every 12 hrs. for 3 days; every 8 hrs. for 6 days; then every 6 hrs.	38.5
M. E.	F	73	Chronic carrier, <i>S. typhosa</i>	12.5	0	0	Asymptomatic, probably source of fatal cases in a nursing home	None		1 yr.	+31	0.25 gm. every 8 hrs.; 2 months later—4 doses of 1.0 gm.; then 0.5 gm. every 6 hrs.	23.0
P. E.	F	26	Enteritis, <i>S. newport</i>	25	+++	101-103	Malaise, prostration, abdominal cramps, diarrhea, nausea, vomiting	Penicillin	3	12	20	0.25 gm. every 6 hrs. for 1 day; then every 12 hrs.	20.0
C. M.	F	51	Enteritis, <i>S. newport</i>	6.3	+++	101	In "shock," dehydrated, severe diarrhea, vomiting and distention	Penicillin	3	12	15	0.5 gm. every 6 hrs. + 20 mg. intramuscularly, every 12 hrs.	7.0 +0.14 i.m.
A. A.	M	68	Bacteremia; osteomyelitis of spine; psoas abscesses, <i>S. cholerae suis</i>	6.3	+++	102-104	Back pain, chills, urinary frequency, incontinence, abdominal distress, cough and disorientation	Penicillin	3	+14	+15	0.5 gm. every 6 hrs. + 20 mg. intramuscularly, every 12 hrs.	21.0 +0.44 i.m.
F. S.	F	80	Bacteremia, source undetermined, <i>E. coli communis</i>	12.5	+++	102 (irregular)	Anorexia, epigastric pain, weight loss, constipation, jaundice, hepatomegaly, epigastric mass	Penicillin	11	?	+15	0.25 gm. every 4 hrs.; then 0.75 gm. every 8 hrs. last 4 days	22.5

TABLE I—Continued

Patient	Bacteriologic Findings*				Clinical Effects				Toxic Effects	Estimation of Effect of Aureomycin		
	Source	Relation to Therapy			Days from 1st Dose Until:			Effect on Symptoms; Other Therapy				
		Before	During	After	Afebrile	Improved	Well					
R. H.	Blood Stool	++	0	0	3	1	8	Distention persisted after general improvement. Transfused on day 12	None	Good		
J. H.	Blood Stool	++	+ 1 day, then 0	0	7	4	8	Vomiting stopped, appetite good and looked brighter after fourth day	Vomited 4 days	Doubtful		
L. O'C.	Blood	+	+ 1 day, then 0	—	5	5	6	Fever declined gradually after aureomycin begun, but improved only after 5 days	None	Good?		
M. O'C.	Urine Stool	0	0	—								
	Blood	+	0	0	20	8	20	Got worse, T 105, for 3 days; diarrhea stopped eighth day; gradually improved. Transfused on days 8 and 9	Vomited early doses†	None		
A. L.	Urine Stool	0	0	—	13	7	13	Improved after 7 days; then severe abdominal pain for 3 days (perforation); intestinal hemorrhage twelfth and thirteenth days. Transfused 4 times	None	None?		
M. E.	Blood	+	+ 6 days, then 0	—	Stool culture positive 1 week after aureomycin begun; all others negative or overgrown by Proteus during therapy. Duodenal drainage, and stools 2 and 3 weeks after treatment ended were positive. Bile cultures positive post-cholecystectomy until after second course was started. Stool cultures again positive after second course ended.							
	Urine Stool	+	0 or Proteus	0								
	Stool	+X15; 0X5	+X1; 0X27	+	2½	3	5	Diarrhea gradually stopped and improvement was then steady	None	None		
P. E.	Duodenum Stool	+	+ 31	+					None	None		
	Bile	+X8	+	0					None	None		
P. E.	Blood	0	0	0					None	Good		
	Urine Stool	+	0	0					None	Good		
C. M.	Blood	0	—	+A	Operation before treatment started, bowel injected and distended. Bowel grossly normal at autopsy							
	Urine Stool	++	+	+A								
A. A.	Blood	+	+	+A	Slight improvement for 3 days, then chills, apathy and confusion returned. Hemoglobin dropped from 16 to 7 gm. Found dead in bed. Autopsy: ruptured aortic aneurysm (see "Diagnosis")							
	Urine	0	—	—								
F. S.	Blood	+X3	+X4; 0X5	—	Improved slightly for 3 days, mass got smaller and then was not felt; appetite improved and icterus cleared. Chills recurred; passed a bloody stool; hemoglobin dropped from 85 to 55% and patient died. No autopsy							

\* + = positive, 0 = negative for causative organisms; A = autopsy; — = not done. The sensitivity of all strains isolated from the same patient before, during and after aureomycin were identical. Numbers after "+", or "0" in columns "During" and "After" = no. of days after treatment begun or ended, respectively.

† Relapse of fever during treatment suggested "drug fever"; test dose of 200 mg. after 10 days caused no fever or symptoms.

‡ Onset indeterminate; acutely ill at least two weeks prior to entry; aureomycin begun four days later.

Patient J. H. (figure 2) was the infant sister of the first patient. She and other members of her family had been given typhoid vaccine by a local health officer while the first patient was still in the hospital. She became ill about three weeks after her brother had been admitted to the hospital and two days after the prophylactic typhoid vaccination. Interestingly enough, a



culture of this patient's stool obtained by the health officer at the time of the vaccination was reported as positive for typhoid by the State bacteriological laboratory. Treatment was begun on the eighth day of illness, after positive cultures for typhoid bacillus had been obtained from both blood and stools in the hospital laboratory. No further blood cultures were obtained from this patient but of the numerous stools that were cultured during and after aureomycin therapy only the one obtained on the second day of treatment yielded typhoid bacilli; the others were either negative for typhoid organisms or were overgrown by proteus. The patient was not severely ill at any time, but definite improvement with a drop in temperature and pulse rate did not occur

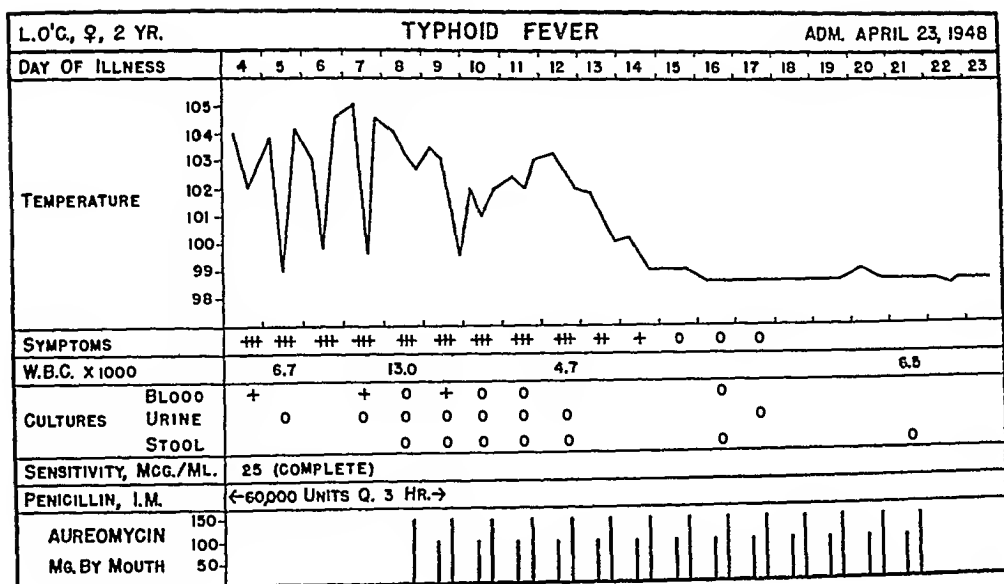
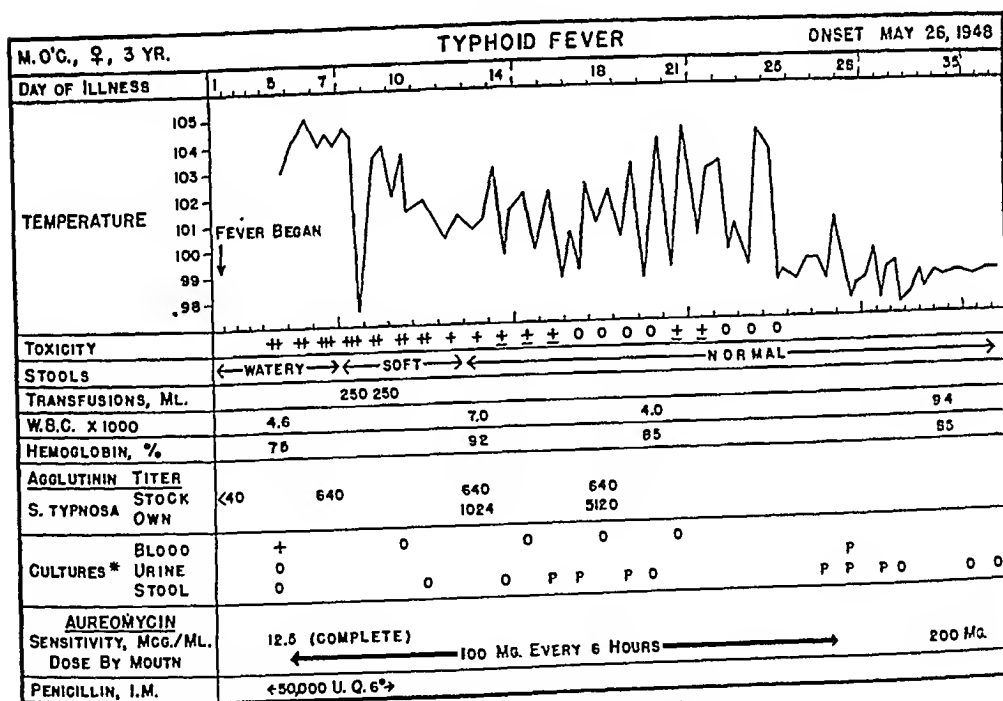


FIG. 3.



\* ++ S. TYPHOSA; P=OVERGROWN BY PROTEUS; 0=NEGATIVE FOR S. TYPHOSA.

FIG. 4.

until after five full days of aureomycin therapy. It was felt that the aureomycin probably did not contribute much to the recovery in this case.

Patients L. O'C. (figure 3) and M. O'C. (figure 4) were members of the same family who were admitted to the hospital about a month apart. Blood cultures were positive before treatment in both of these patients and were all negative after treatment was begun except for one positive culture

It was difficult to ascribe any great benefit to aureomycin in these two cases although the favorable course during and after aureomycin, particularly in L. O'C. and the persistently negative cultures after the second day of treatment does not exclude the possibility that aureomycin was of benefit. It should also be noted that, except for the fever in M. O'C., all four of these patients were asymptomatic by the end of the second week of the disease.



FIG. 5.

In A. L. (figure 5) treatment was undertaken during a relapse of fever that was accompanied by severe symptoms and positive cultures of the blood and stools. This relapse occurred after almost a week during which the patient had been afebrile, had negative blood cultures and was essentially

free of symptoms except for some diarrhea. The patient remained severely ill and continued to have positive blood cultures and severe diarrhea throughout the first week of aureomycin treatment. Thereafter he improved rapidly and blood cultures became and remained negative. During the period when his fever was declining the patient had severe abdominal pain and tenderness suggesting a perforation of the bowel but operation was withheld because of the marked improvement in the patient's general condition. He later passed some grossly bloody stools and was given transfusions. The aureomycin was continued throughout these episodes and improvement thereafter was steady. Stool cultures were positive before and on the first day after treatment was started but typhoid bacilli could not be identified in cultures of subsequent stool specimens, many of which, however, were markedly overgrown with proteus. Urine cultures in this patient were negative before treatment but the patient developed a lower urinary tract infection with *Proteus vulgaris* during a period when he was delirious and had an indwelling catheter. The bladder infection was mild, but persisted despite the aureomycin treatment until after the catheter was removed and other therapy was discontinued.\*

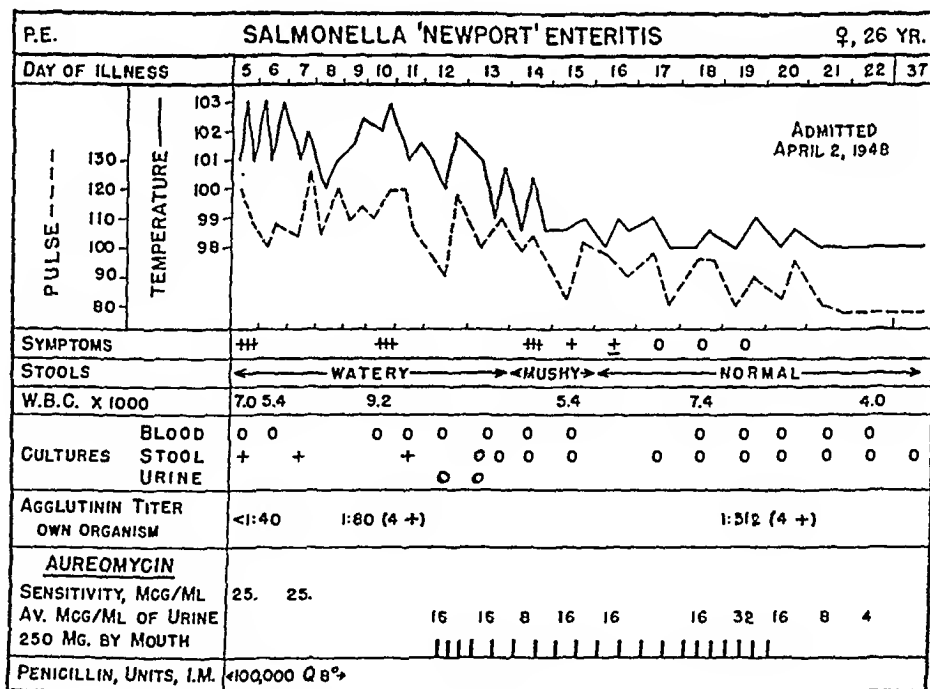


FIG. 6.

*Salmonella Infections.* Three patients were treated for severe salmonella infections. In P. E. (figure 6) aureomycin treatment was begun on the twelfth day of the disease when the patient was extremely ill with fever.

\* *P. vulgaris* has proved most resistant to aureomycin in vitro and in vivo.<sup>2, 4</sup>

prostration and intense watery diarrhea and abdominal cramps. Blood cultures were all negative in this patient but cultures of three stools obtained before aureomycin treatment was begun were positive for *Salmonella newport*. The patient's temperature and pulse rate began to fall gradually and the abdominal cramps ceased soon after treatment was started. The stools became less frequent and less watery after the second day and were essentially normal two days later when the patient became and remained afebrile. All cultures of blood, stool and urine were negative for salmonella after treatment was started. Improvement in this patient coincided with the beginning of aureomycin treatment and may have been attributable to this therapy.

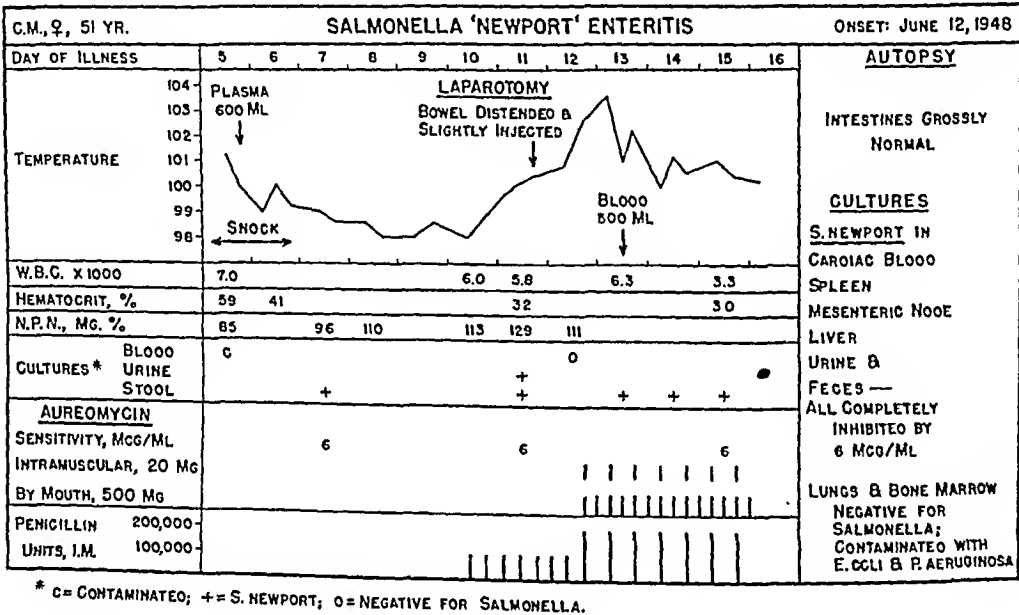


FIG. 7.

Patient C. M. (figure 7) was admitted on the fifth day of an extremely severe illness accompanied by constant vomiting and diarrhea. She had been markedly dehydrated and "in shock" with abdominal distention, rapid, thready pulse, low blood pressure, cyanosis and sweating for about 24 hours prior to entry. On arriving at the hospital the patient was treated symptomatically with fluids and plasma infusions. The cause of the symptoms was not apparent and in view of the persistence of the diarrhea, vomiting and distention the possibility of intestinal obstruction was considered. After much hesitation on the part of both internists and surgeons the patient had an exploratory laparotomy which showed no obstruction or other pathology that could account for the symptoms. Soon after the operation, however, cultures of one of the stools obtained earlier were reported as yielding a salmonella which was later identified as *Salmonella newport*. Additional cultures of blood, stools and urine were then taken and the patient was started on aureomycin by mouth and intramuscularly. The blood culture

was negative but the urine and stool cultures were positive for *Salmonella newport* and three additional stool cultures taken during the course of treatment were also positive for the same organism. Intramuscular penicillin was begun before the operation and was later continued because of signs that suggested the presence of congestion or infection in the lung. The patient failed to rally and died on the fourth day of aureomycin treatment.

At autopsy, there was moderate distention and some injection of the serosa and mucosa of the jejunum, the walls of which were soft and friable, but there were no hemorrhages. The rest of the bowel was grossly normal. Microscopic sections of various parts of the intestine all showed marked edema of all the layers with mild congestion of the vessels. There were also scattered foci of chronic inflammation in the submucosa of the ileum and colon. The mesenteric nodes showed some edema. There was vacuolization of all of the lining cells of the proximal tubules of the kidney which was interpreted as some kind of nephrosis. Autopsy cultures of blood, urine, feces and several organs yielded *Salmonella newport*.

Obviously, the aureomycin had no beneficial effect in this case, but the treatment may have been inadequate and was undertaken too late.

Patient A. A. (figure 8) was also acutely ill and in poor general condition on arrival at the hospital. The symptoms in this patient were referable to the mid-back and suggested a renal infection, but the urine was essentially normal and was negative on culture, and the blood nonprotein nitrogen was only slightly elevated. Blood cultures obtained before and during 11 days of oral and intramuscular therapy were all positive for *Salmonella suispestifer*. The patient had a steady drop in hemoglobin during this time but there was

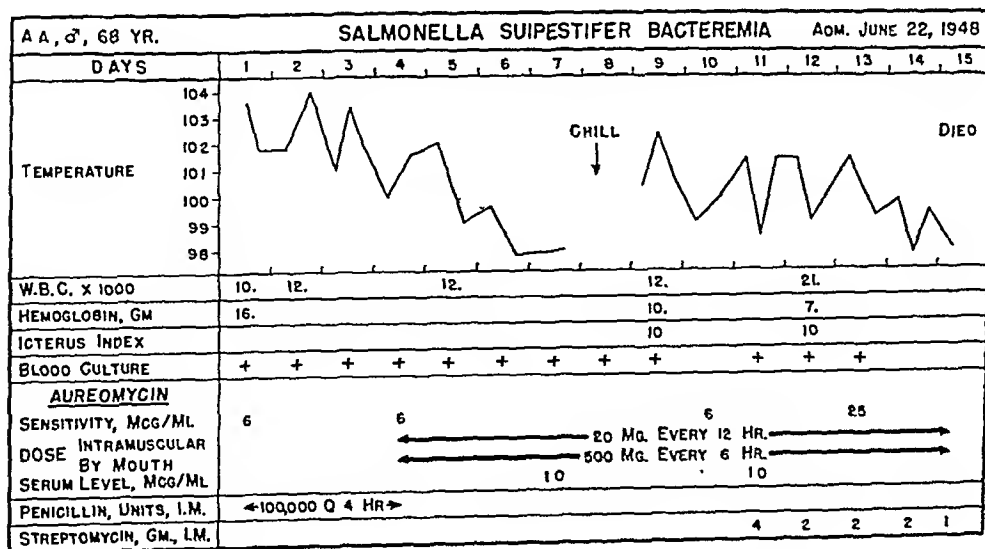


FIG. 8. This patient died of a ruptured aneurysm of the abdominal aorta. Autopsy also revealed bilateral psoas abscesses communicating with an intervertebral abscess in the lumbar spine. The cardiac blood, liver and pus from the abscesses all yielded positive cultures for *S. cholerae suis*. There was also a vegetation on one of the tricuspid valves, but a culture of this vegetation yielded no growth.



no evidence of bleeding from the bowel, and blood studies failed to reveal any evidence of intravascular hemolysis. Cultures of the stools failed to yield salmonella. The patient's general condition remained the same, but he died quite suddenly. Autopsy showed the death to be due to a ruptured aneurysm of the abdominal aorta with considerable extravasation into the retroperitoneal space. There were also large bilateral psoas abscesses communicating with an intervertebral abscess, the latter probably resulting from an osteomyelitis of the spine. *Salmonella cholerae suis* was obtained at autopsy from cultures of cardiac blood, pus from the abscesses, liver and other organs.

In this patient there was no evidence of any beneficial effect from the aureomycin on the local or systemic infection. Streptomycin was also given during the last four days without influencing the course of the infection.

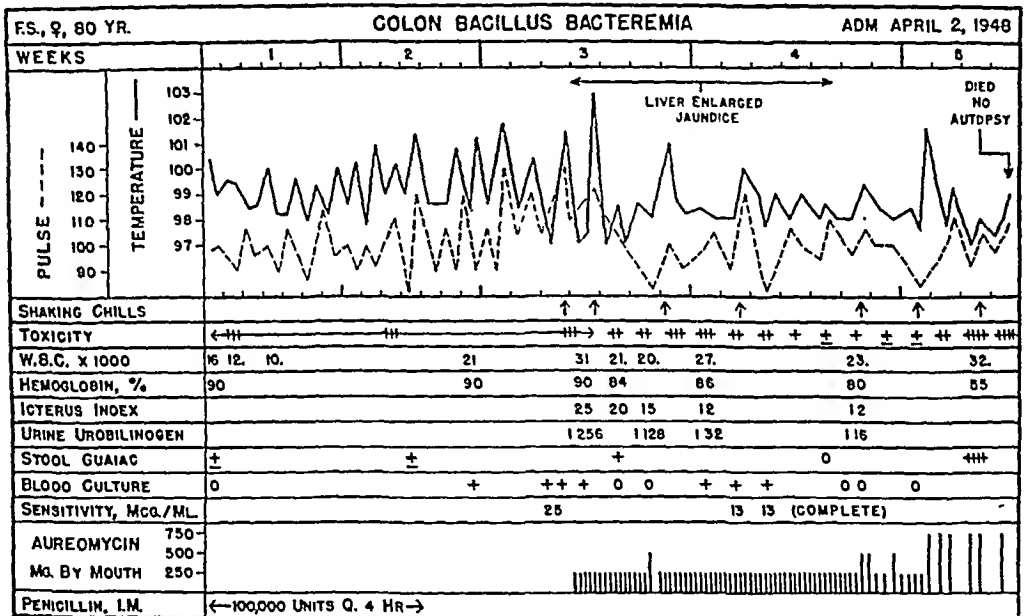


FIG. 9. This patient died following a large intestinal hemorrhage. The nature of the underlying disease and the source of the bacteremia were not determined.

*Colon Bacillemia.* Patient F. S. (figure 9), who had a colon bacillus bacteremia of undetermined origin, was acutely and chronically ill and had evidence of infection in the abdomen probably superimposed on malignant lesions. This patient showed some symptomatic improvement during aureomycin treatment with appreciable reduction in the size and tenderness of the liver and of the abdominal masses which were present. She did, however, have several chills and positive blood cultures during the aureomycin therapy. When the patient appeared to be sufficiently improved to permit further studies of the nature of the infection, she suddenly had a large intestinal hemorrhage and died. There was no autopsy so that the nature of the underlying disease was not determined. The temporary improvement in this pa-

tient may be attributable to the antibiotic, but the failure to sustain this effect was probably due to the presence of foci of suppuration that were unaffected.

*Typhoid Carrier.* Patient M. E. was a known carrier of typhoid bacilli for at least a year and was the probable source of an outbreak of typhoid fever in a nursing home which resulted in two deaths. At various intervals between August 1947 and April 16, 1948, 20 different stool specimens were cultured and 15 of them yielded typhoid bacilli. She was treated for 31 days with doses of 0.25 gm. of aureomycin by mouth every eight hours and stools were cultured daily during this period. Only one of them, obtained on the eighth day of therapy, was positive for typhoid bacilli; 22 were negative and seven were overgrown with proteus organisms so that typhoid bacilli, if present, could not have been detected. On the last day of treatment, duodenal drainage was carried out through a Levine tube and cultures of the drainage material yielded typhoid bacilli. In subsequent cultures of stools, typhoid bacilli were again obtained on June 1 and 8, two and four weeks respectively after the course of aureomycin treatment was ended. It was, therefore, evident that aureomycin alone had not accomplished the desired effect.

The patient had a cholecystectomy performed on July 19, and cultures of the contents of the gall-bladder and of the common duct bile obtained at the operation were both positive for typhoid bacilli. Biliary drainage was then carried out through a T tube and daily cultures of the biliary drainage fluid continued to be positive. On July 26, the patient was again started on aureomycin by mouth; 1 gram was given every six hours for four doses and then 0.5 gram every six hours until August 4. Cultures of bile were positive before the first dose and again on July 27 but they were negative on July 28 and thereafter. Stool cultures failed to yield typhoid bacilli during the second course of aureomycin, but many of them were overgrown by proteus. The stools again became positive one week after the aureomycin was stopped.

Tests made with bile obtained from this patient on many occasions before and during the aureomycin treatment indicated that the bile itself did not inactivate aureomycin when added to a solution of the antibiotic in vitro. It was not possible, however, at any time during the treatment to demonstrate aureomycin activity in bile obtained from the T tube even when care was taken to test for this activity promptly after the bile was obtained.

### TOXICITY

Except for possible drug fever in L. O'C., there was no evidence of any toxic effects attributable to aureomycin in any of these cases. Patients J. H. and M. O'C. vomited some of the early doses, but they had been vomiting more or less constantly before the treatment was started. It is of interest that the diarrhea that was present in some of these patients improved while they were taking aureomycin. In other groups of cases, the occurrence of large bulky stools was almost the only untoward effect from oral aureomycin.<sup>1,4</sup> There

was no evidence of any toxic effects on the blood, kidney or liver in any of these patients and no rashes were observed.

### DISCUSSION

The present cases indicate quite clearly the need for caution in interpreting the results of the use of any new therapeutic agent in many infectious diseases. The results of therapy in two of the patients with typhoid fever, R. H. and L. O'C., and in one of those with salmonella infection, P. E., could be considered as indicating definite beneficial effect from aureomycin. These patients began to improve within a day or two of the time when the antibiotic was begun, and all of their cultures were negative for the causative organisms after treatment was started, except for one positive blood culture obtained after 18 hours in patient L. O'C. The course of events in two of the other typhoid patients, J. H. and M. O'C., likewise could be interpreted as showing some favorable effect in that improvement, both clinical and bacteriological, began after treatment was started and was progressive, though slow, thereafter. The persistent fever in the case of M. O'C. was not accompanied by any relapse of symptoms. Even in the case of patient A. L. who was so severely ill and continued to have positive blood cultures throughout the first week of treatment, it was felt that the aureomycin may have had some favorable effect in limiting the severity of the illness and may possibly have averted what was expected to be a fatal outcome.

The failures to influence the clinical course or the bacteriological findings of the salmonella enteritis in patient C. M. may, of course, have been due to the fact that treatment with aureomycin was undertaken when the disease was far advanced and the patient already had renal failure with nitrogen retention, possibly resulting from the dehydration and shock. In the case of A. A., on the other hand, while the death was not directly attributable to the infection, the failure to control the latter was associated with the presence of large foci of suppuration that were not detected before death. The same was probably true in the case of the colon bacillus bacteremia, although absolute proof for this is lacking. The failure to eliminate the carrier state in M. E. before the cholecystectomy was performed may also have been due to the inability of aureomycin to influence the focus in the gall-bladder. Furthermore, it was not possible later to detect aureomycin activity in the bile of this patient while she was receiving fairly large doses of the antibiotic by mouth. The failure in this case may be attributable to persistence of infection in the liver and bile ducts and the failure of the antibiotic to clear these foci of the organisms.

It can only be concluded that the effects of aureomycin in the present group of cases leave much to be desired. The possibility cannot be excluded that the use of larger oral doses, or parenteral therapy in proper doses may have a better effect in such cases.

The recent preliminary report of favorable effects from chloromycetin on typhoid fever,<sup>11</sup> when carefully scrutinized, also does not give unequivocal evidence of benefits ascribable to that antibiotic. The types of cases, severity and other details are not given in this preliminary report. These details and the results in additional cases, particularly severe and late cases, are awaited before final judgment of the effects of this agent can be made.

### SUMMARY AND CONCLUSIONS

The relevant features in five cases of typhoid fever, three of severe salmonella infections, a case of colon bacillus bacteremia and a typhoid carrier that were treated with a new antibiotic, aureomycin, have been presented. The clinical and bacteriologic findings in some of these cases suggested that the aureomycin had some beneficial effects, but the results, in general, were not striking. Concealed foci of suppuration may have been responsible for some of the failures.

*Addendum.* Two additional cases of typhoid fever treated since this paper was submitted are worth mentioning:

M. F., a white woman 39 years old, was started on aureomycin therapy on the ninth day of illness. She was acutely ill and disoriented, with fever ranging between 103 and 105°, nausea, vomiting, diarrhea, repeated showers of rose spots and an enlarged liver. She had received 5 gm. of sulfathalidine every four hours and a million units of penicillin every three hours for seven days but her clinical condition failed to improve on this regime, and on the night of the eighth day, she suffered a massive intestinal hemorrhage. Other chemotherapeutic agents were then discontinued and aureomycin was given in doses of 1 gm. orally every four hours. After four days, the dose was gradually reduced to 2 gm. daily and she received a total of 90 gm. in 25 days. The patient improved promptly after the aureomycin was started. The temperature fell to normal by lysis during the course of one week; no further rose spots appeared; the diarrhea abated; no further intestinal hemorrhage occurred, and the stools became normal in the space of a few days. Repeated blood, urine and stool cultures were negative for typhoid bacilli during the aureomycin treatment and for three weeks thereafter with the exception of a single positive stool reported on the twenty-third day of treatment; on the same day, however, bile obtained by duodenal drainage was negative for typhoid bacilli.

H. W. K., a white male of 29, was started on treatment with aureomycin on the seventh day of a severe relapse of typhoid during which he was having repeated chills, fever sustained at 105 to 106° F., delirium, rose spots, nausea, intense diarrhea, jaundice and positive blood and stool cultures in spite of treatment with 6 gm. of sulfadiazine and 8,000,000 units of penicillin daily. This therapy was then discontinued and 0.5 gm. of aureomycin was given every four hours. Within 12 hours the temperature dropped to 101° F., and then gradually to normal over the following week; the patient's sensorium cleared; no further rose spots appeared; stools became less frequent and semi-formed and then formed; jaundice cleared; and all cultures of blood, urine and stools were negative after the treatment with aureomycin was started.

In M. F., aureomycin seemed to have a definite beneficial effect, although the significance of the single positive stool culture during treatment is not clear. In H. W. K. it was felt that the clinical and bacteriological improvement was definitely related to the aureomycin therapy. The findings in the latter case are in sharp contrast to those in patient A. L. (figure 5) in whom the course prior to aureomycin was very similar, but smaller doses of aureomycin were used and the bacteriological and clinical recovery were considerably more delayed. These two cases, however, serve only to reemphasize the difficulty in evaluating the efficacy of this agent even when relatively large doses are used by mouth.

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## INFECTIOUS ARTERITIS \*

By WILLIAM S. MIDDLETON, F.A.C.P., *Madison, Wisconsin*

THE anatomico-physiological relationships of arteries presuppose not only their normal nutrient responsibility but also repeated exposures to adverse influences, such as physical, chemical, toxic, and infectious, that affect tissues and organs generally. The degenerative conditions of the arteries have received increasing attention in the laboratory and the clinic in recent years. The inflammatory states of these vessels have not been accorded proportional attention. In fact the clinical appreciation of infectious arteritis has lagged far behind the advances in the knowledge of the pathogenesis and pathology of this significant group of vascular injuries.

The arterial walls may be the seat of degenerative changes in the course of a number of infectious diseases. Fatty degeneration in the intima and media may occur in typhoid fever, brucellosis, scarlet fever, pneumonia, and diphtheria. These degenerative changes may be attended by a subintimal proliferation. Although this reaction is non-specific, the vascular injury may lead to rupture and severe hemorrhage. Rarely does arterial thrombosis attend this lesion. The histologic common denominator of a fibrinoid degeneration of collagen has led to an interesting grouping of lupus erythematosus disseminatus, dermatomyositis, scleroderma, and Libman-Sacks' syndrome.<sup>1</sup> Baehr and Pollock<sup>2</sup> stress the fallacy of too close analogies on this ground and on the basis of clinical dissimilarity separate rheumatic fever, rheumatoid arthritis, serum sickness, periarteritis nodosa and thromboangiitis obliterans from disseminated lupus erythematosus and scleroderma. Certain fine points of microscopic differentiation, as the "wire loop" lesion in the glomeruli in lupus erythematosus disseminatus, might be invoked<sup>3</sup>; but for present purposes Klemperer's position<sup>4</sup> of the non-specificity of diffuse collagen diseases with an incidental vascular involvement excludes their consideration in this relation.

Inflammation of the arteries may occur by continuity. Yet the arterial wall must have a high degree of tissue resistance, since in many instances arteries traverse zones of virulent infection and active inflammation without intrinsic involvement. However, the arteries may be attacked by infections from within or from without. By the former route a septicemia is usually responsible. In plague, for example, the blood stream may be heavily seeded with *Pasteurella pestis* and the vascular injury be widespread. In pyogenic infections a septic embolus is the source of a local vegetative endarteritis, which may lead to a mycotic aneurysm or to rupture with more or less serious results. If the invasion be from without, a periarteritis with in-

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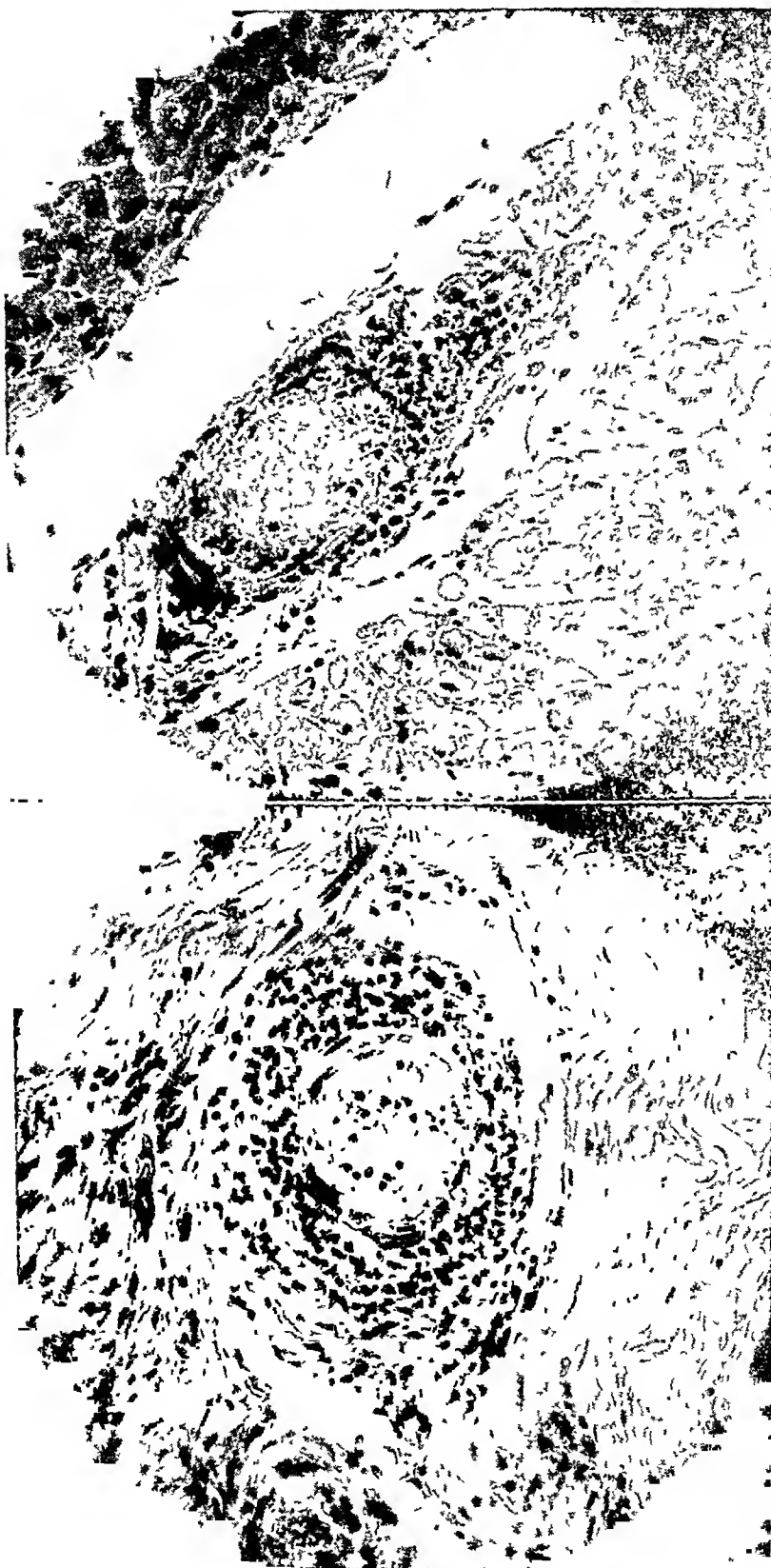
From the Department of Medicine, University of Wisconsin Medical School.

volvement of the adventitia, media, and intima in sequence may be anticipated. The perivascular lymphatics may bear the infective organisms to the arteries. The cellular infiltration may similarly weaken the wall with disastrous effects. Whether perivascular or endovascular, lesser degrees of reaction may lead to thrombosis. To project the functional consequences of such lesions, the nutritional changes incident to such encroachments upon vascular channels may well persist after the clinical subsidence of the pathologic process.

In general the pathogenesis of infectious arteritis depends upon the direct invasion of the vessel by the etiologic agent. A further important mechanism, hyperergy to streptococci, was suggested by Swift, Derick, and Hitchcock<sup>5</sup> in explanation of the rheumatic lesions. Gruber<sup>6</sup> had earlier advanced the same thesis for the pathogenesis of periarteritis nodosa. Rössle<sup>7</sup> broadened this concept by indicating the non-specificity of the etiology for periarteritic reactions. Clark and Kaplan<sup>8</sup> observed analogous changes in mesenchymal tissues with periarteritis and necrotizing arteritis after large doses of antipneumococcus serum. More recently Rich<sup>9, 10</sup> and his associate Gregory have demonstrated beyond peradventure the dependence of periarteritis nodosa upon sensitivity. Interesting has been the incrimination of sulfonamides in this relation.

The rickettsial diseases afford the best examples of widespread vascular injury in the course of acute infections. The primary reaction to the *Dermacentroxenus rickettsi* of Rocky Mountain spotted fever is a swelling and proliferation of the endothelium of the capillaries, arterioles, and veins. Perivascular infiltration with monocytes, lymphocytes, and plasma cells occurs. The rickettsiae are abundant in the endothelium and the muscularis media of the affected vessels. Thrombosis is common and may lead to gangrene of the soft palate, ears, nose, fingers, toes, buttocks, prepuce, scrotum, and vulva. In a word the basic lesion of Rocky Mountain spotted fever is an infectious endangiitis (figures 1a and b). The skin and the central nervous system are predominantly involved, but the vessels of the thyroid gland, gastrointestinal tract, myocardium and skeletal muscles are occasionally affected. Hemorrhages into the skin, subcutaneous tissue and testis, with the described gangrene, constitute the sole gross lesions.

The cutaneous manifestations of Rocky Mountain spotted fever strongly suggest their vascular background. The early macular eruption over the wrists, ankles, and back becomes generalized. Subcuticular blotching depends upon an interference with the circulation in the deeper layers of the skin. Extravasation of blood into the eruption puts an end to blanching on pressure. Duskiness of the dependent legs and edema of the hands and feet reflect venous impairment or deep thrombosis. Gangrene is a frequent sign of more serious arterial involvement. The eruption, upon fading, may leave a residual pigmentation which lights up on vascular dilatation or pales upon vasoconstriction long after convalescence. Desquamation is not an infrequent sequel to the eruptive phase. Reflecting the predilection for the central



(a) Skin

(b) Myocardium

FIG. 1. Histologic lesions of Rocky Mountain spotted fever.



nervous system, restlessness and insomnia may obtain. Delirium may give way to coma. Photophobia, stiff neck, muscle resistance, positive Kernig sign, and convulsions may suggest meningeal involvement. Cloni, paradoxical reflexes, deafness, and speech involvement may imply focalization, but with few exceptions these neurological signs are transitory.

Periarteritis nodosa has been one of the most elusive of the diseases attended by serious vascular injury. Recent studies <sup>7, 8, 9, 10</sup> have elucidated certain aspects of its pathogenesis. Hyperergy undoubtedly plays a major rôle in its initiation. Infection, rheumatic, streptococcal and pneumococcal, <sup>6, 7, 11</sup> has been incriminated in this relation. Serum sickness <sup>8, 10</sup> and hypersensitivity reactions to chemicals <sup>9, 10</sup> are other cogent bases for this astounding pathologic picture. The histologic sequence suggests a perivascular lymphatic portal. The fundamental changes include necrosis of the media and fibrino-cellular infiltration of all coats of the involved vessel. Lymphocytes, plasma cells, and eosinophiles dominate the cellular exudate. Proliferation of the lining endothelium follows. This intimitis leads to thrombosis in many instances. With organization these thrombi become canalized. With disintegration of the muscularis and the elastic lamina tiny aneurysmal protrusions may ensue. Fibroblasts are replaced by fibrous tissue as repair advances. The encroachment upon the local nutrition may induce atrophy, degeneration, infarction, gangrene, and scarring (figure 2).

The distribution of periarteritic lesions is singularly bizarre and irregular. An isolated vessel may be involved; but contrary to the earlier opinions temporal arteritis may at times be a superficial manifestation of a widespread involvement.<sup>12</sup> These circumstances, together with the several stages of the pathologic process in the same subject, presage an inconstant clinical picture. However, all symptoms and signs are directly traceable to the inflammation, disintegration, and repair of the arterial tree. Indeed, the impairment of nutrition may be much greater in the stage of repair than in the active inflammation. The diagnostic tetrad of Meyer<sup>13</sup> and Brinkmann,<sup>14</sup> chlorotic marasmus, polyneuritis and polymyositis, vague gastrointestinal disturbances and nephritis, affords an excellent spring-board for the clinical diagnosis. The muscular and neural manifestations are directly attributable to the periarteritic lesions. Invasions of the coronary bed may lead to thrombosis. Bronchial asthma may occur in a causal or incidental relationship. A variety of symptoms and signs attends the involvement of the abdominal arteries. Among these the predilection for the vessels of the gall-bladder may bring the strong suspicion of acute cholecystitis in its train. Duodenal ulceration with all of its clinical picture may arise from periarteritis nodosa. Diabetes mellitus may reflect pancreatic involvement. A rising blood pressure with the evidences of renal insufficiency bespeaks an extensive invasion of the arteries of the kidney. Nor would a recital of the central nervous and cutaneous manifestations exhaust the clinical potentialities of this condition. Most important in the recognition of periarteritis nodosa is a diagnostic awareness. A wide dispersion of vague symptoms and signs in a septic



(Courtesy of Dr Norman J Sweet, San Francisco)

FIG. 2. Histologic lesion of periarteritis in the liver. Left  $\times 15$ ; right  $\times 40$ .

patient should suggest the diagnosis, since only by a diffuse vascular process could such a clinical picture develop. Eosinophilia, among other laboratory findings, is a further signpost to its consideration.

Although other etiologic factors have been invoked, thromboangiitis obliterans would seem to be infectious or allergic in origin. Essentially a disease of the extremities, it is also encountered in the cerebral, coronary, mesenteric, and renal arteries. The moderate sized arteries of the leg are more commonly involved than those of the thigh. A minority of sufferers from this disease undergo invasion of the arteries of the arm. Intimal proliferation usually initiates the pathologic process. Occasionally the adventitial infiltration is primary. In the acute phase lymphocytic and neutrophilic invasion of all coats of the artery may be observed. Giant cells may appear. Significantly the arterial changes are segmental and considerable spans of an affected vessel may escape. Thrombosis occurs at the site of vascular inflammation. These thrombi contain inflammatory cells but tend to undergo organization after fibroblastic infiltration. Canalization of the thrombus follows and mere slits of tiny communicating lacunae promise a meagre approximation to the pre-inflammatory nutrition for the involved part. The veins of the leg become similarly involved. Migratory phlebitis is the rule. In spite of the segmental involvement recurrences of inflammation insure progressive circulatory incompetence in the part in most instances. Eventually the involved artery, vein and nerve become incorporated in a single inseparable cord (figure 3).

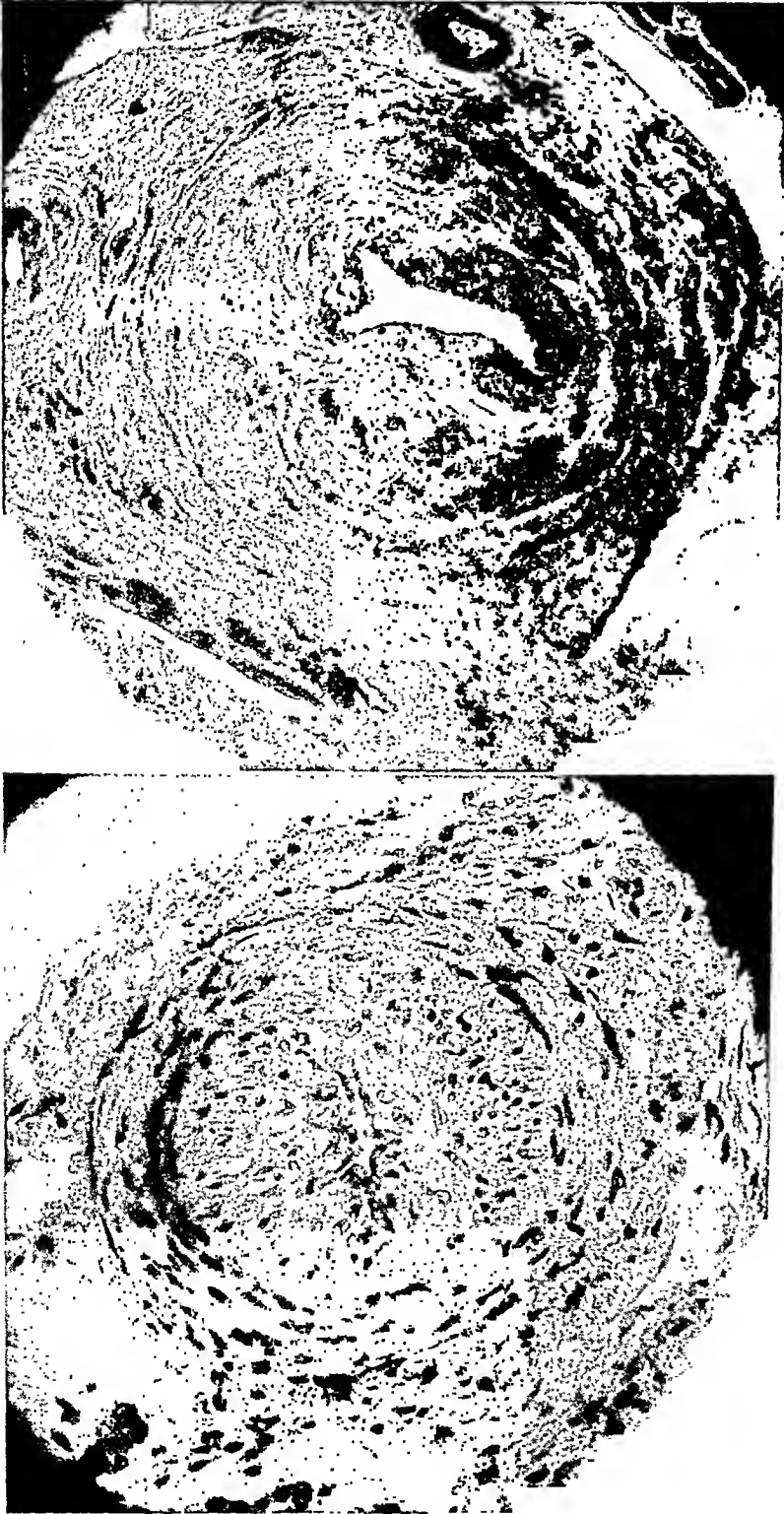
Thromboangiitis obliterans first reflects itself clinically in unusual coldness, paresthesias, pallor and cyanosis upon exposure to cold. This circumstance may mean unusual vasospasm to ordinary stimuli in susceptible vessels. Muscular weakness and aching pains on effort may early result from vascular encroachment. With the advancement of this process intermittent claudication may give place to rest pain. Changes in the color, temperature, texture and pulses of the part all reflect the degree of arterial injury. Anginal episodes may anticipate occlusive symptoms in coronary involvement. Quantitative measurements of the peripheral vascular integrity are now available. By release of sympathetic spasm the degree of actual organic change in the arteries of the extremities can be estimated. Such studies will disclose impairment of the peripheral circulation long before trophic ulceration and gangrene mark the final, irreversible stages of the disease. Furthermore, the intrinsic control of the arterial tone may persist or be resumed after radical sympathectomy.

The rheumatic state is still incompletely understood. Several material gaps in the complete picture remain unfilled. The streptococcus is presumed to be the etiologic agent and a bacterial hypersensitivity has been invoked in its pathogenesis. Certainly from a clinical standpoint this thesis finds substantial support. Furthermore on this basis its common chronicity and its far flung pathologic expressions find much readier explanation than in the older theories. The Aschoff body is the specific histologic unit of the rheu-



FIG. 3. Histologic changes of thromboangiitis obliterans in vessels of leg.

matic state. Always this characteristic agglomeration is closely associated with arterioles. The fibrinoid swelling of the ground substance anticipates the cellular reaction, but it is not specific to the disease. In the vascular injury of the rheumatic state the lesions are widely scattered and variant in intensity. The arteries may be involved in many organs and tissues. Again only isolated branches within a given organ are affected. Endothelial swelling with exfoliation suggests luminal invasion. Thrombosis is rare in rheumatic arteritis. A fibrinous exudate may infiltrate the arterial wall and invade the supporting tissues with a loss in the continuity of the elastica. Thereupon necrosis of the wall with extravasation of blood may ensue. The cellular reaction is neutrophilic and macrophagic. Lymphocytes, plasma cells, occasional eosinophiles and young fibroblasts complete the zone of cellular reaction. Whereupon there occurs an astounding revascularization. New vascular channels appear in the described fibrinous exudate in the walls of the affected artery. As this exudate disappears the muscularis is lost and the elastic laminae are approximated (figure 4a and b). Rheumatic aortitis arises through involvement of the vasa vasorum. Lymphocyte and plasma cell infiltration of the adventitia leads to medial ischemia. Linear fibrosis may impair the elastic and muscular coats but rarely is there serious injury comparable to syphilis.



(b) Coronary

FIG. 4. Histologic changes of rheumatic arteritis.

(a) Pulmonary

Rheumatic fever has lost its old connotation of a disease limited to the synovial and serous membranes and the heart. Few tissues escape its wide attack. Singularly by the terms of its hyperergic pathogenesis, such sensitized subjects are doomed to recurrent, if not continued, onslaughts of the disease. Not only is its victim crippled in the extent of its initial involvement, but there is also the threat of an extending handicap from the vascular encroachment of healing. The initial verrucose vegetations of rheumatic valvulitis eventually undergo cicatricial contraction with resultant insufficiency and stenosis. Contributory to the permanent changes in the valves are the nutritional disturbances of arterial injury—and the coronary arteries, probably, never escape rheumatic involvement. Furthermore, by the same token, the myocardium feels the weight of rheumatic infection and progressive or deferred myocardial fibrosis may be predicted. In general clinicians have a sound viewpoint relative to the gravity of the ultimate prognosis of rheumatic heart disease. Its explanation resides in the insidious order of the rheumatic invasion and repair. Acute and recurring episodes leave residua that pyramid the functional handicap of the original attack.

Syphilis is admittedly a vascular disease. The spirochetes enter the vessel by way of the vasa vasorum or the perivascular lymphatics and the lesion in the smaller arteries is primarily periarteritic. A collar of lymphocytes and plasma cells encircles the involved vessels. Occasionally a distinct gumma is discerned. Medial involvement induces atrophy of the muscularis. Endothelial swelling with proliferation appreciably reduces the lumina of the small arteries (figure 5). Aneurysmal dilatation on a syphilitic background is unusual in the muscular arteries in contrast to its high incidence in syphilis of the aorta, where the disintegration of the preponderant elastica establishes the susceptibility to dilatation. Thrombosis may attend the intimal injury.

During the period of clinical latency some inflammatory changes persist in the vascular system. Lymphocytes and plasma cells resist the encroachment of the spirochetes from the perivascular lymphatics. The endarteritic process advances inexorably and the illusion of arrest may be shattered by delayed evidences of nutritional disturbance and degeneration in the parts supplied. While any viscus may be involved, the leptomeninges and aorta afford the most classical examples of late syphilitic involvement. Significantly the delay in clinical manifestations resultant upon such invasion can more properly be attributed to local tissue resistance than to deferred pathologic reaction.

"Their slow combined inflammatory degeneration *ages the patient* by inducing a premature fibrosis, and it threatens physical integrity and impairs the functional capacity of his vital structures by destroying their vital substances and replacing it with connective tissue."<sup>15</sup> Precocious cerebral accidents suggest a syphilitic etiology. In cerebral vascular involvement alterations in the habit of thinking, irritability, psychic changes and obscure head-



FIG. 5. Histologic lesion of syphilitic arteritis (leptomeninges).

aches or vertigo may anticipate the vascular accident. Visceral involvement elsewhere may encompass the whole gamut of symptomatology.

In summary, the problem of infectious arteritis may be assessed as involved and neglected in the main.<sup>16</sup> The order of histologic changes of the arterial tree gives the clue to the route of invasion. The clinical course of certain diseases depends predominantly upon the specific inflammatory arteritis. In others its place is subsidiary. The reparative stage of certain forms of infectious arteritis may be more significant than the active inflammation. Infectious arteritis forms the dominant feature of the rickettsial diseases, periarteritis nodosa, and thromboangiitis obliterans. In all of these diseases the entire picture may be interpreted in terms of the extent and the degree of the vascular injury. The acute inflammatory phase of the infectious arteritis determines the clinical expression of the rickettsial diseases and its subsidence marks the period of recovery in their course. Undoubtedly permanent changes in the smaller arteries remain as relics of their earlier inflammation, but in the main they are unimportant. Periarteritis nodosa and thromboangiitis obliterans are characterized by just as specific vascular changes, but importantly in these diseases the processes of repair determine even more serious nutritional changes in the involved part than

does the acute infectious phase. Rheumatic fever and syphilis represent a somewhat different situation. The inflammatory stage of the infection is not frequently an independent dominant feature of rheumatic origin; nor is the vascular injury prone to induce aneurysmal dilatation in the small vessels. The effects of rheumatic and syphilitic arteritis are dependent upon long continued subnutrition with degeneration and fibrosis rather than the pathological changes of the acute vascular damage.

*Note:* Grateful acknowledgment for the preparation of the photomicrographs is made to Drs. J. C. McCarter and J. J. Lalich.

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# CORAMINE (NIKETHAMIDE) IN BARBITURATE POISONING: COMPARISON WITH PICTO-TOXIN; PRELIMINARY REPORT \*

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RECENTLY a marked increase in the number of cases of poisoning due to barbituric acid derivatives has made an effective antidote or analeptic a matter of paramount importance. The drugs of the barbiturate group have been readily available to the laity, and newspaper publicity, instead of helping the situation, appears actually to have increased the number of cases of attempted suicide from these drugs.

Various antidotes for human barbiturate poisoning have been in use for years. Picrotoxin and coramine (as coriamyrtin) were used as early as 1891-1892.<sup>1</sup> Arnett<sup>2</sup> administered picrotoxin in 1933 after Maloney, Fitch and Tatum<sup>3</sup> had demonstrated its effectiveness in animal experiments. Koppanyi<sup>4</sup> used it extensively in 1936. Burdick and Rovenstine<sup>5</sup> in 1945 claimed picrotoxin to be the drug of choice in barbiturate poisoning. Unfortunately this has tended to result in the neglect of other drugs, one of which, coramine, we believe to be equal to, if not superior to picrotoxin.

In order to demonstrate the practical use of coramine in those barbiturate intoxication patients having a degree of narcosis approaching lethal levels, to establish the proper dosage, to determine the margin of safety, and to establish important prognostic criteria in these poisoned patients, the study of this analeptic drug was undertaken. Throughout the study, coramine was compared with picrotoxin. No attempts were made to use metrazol, amphetamine sulfate, strychnine or any combination of these in this series. The cases were graded as to the depth of narcosis, since too many reports make no effort properly to evaluate this factor.

The cases were divided into two groups: those patients admitted to the hospital on even numbered days were treated with coramine, and those admitted on odd numbered days were treated with picrotoxin. A few cases received both coramine and picrotoxin, when heroic measures were thought necessary. In 1945 and 1946, a total of 58 cases were treated, with five deaths. From 1941 to 1945, there were 41 cases with three deaths, a total of 99 cases with eight deaths in five years.

Coramine (also known by the official non-proprietary name of Nikethamide) is pyridine betacarboxylic acid diethylamide, a yellowish liquid, freely soluble in water. The ordinary ampule is 1.5 c.c. of 25 per cent solution. In 1892 Koppen<sup>1</sup> reported its use in the counteraction of narcosis under the name of coriamyrtin. Coriamyrtin occurs in several species of the plant

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Coriaria, of which the best known is *Coriaria myrtifolia* or currier's sumach. (Coramine as used today is a synthetic compound, not the extract of Coriaria as originally used.) Further investigations in European countries were reported by Uhlman,<sup>6</sup> Guth,<sup>7</sup> Schubel and Gehlen.<sup>8</sup> Kennedy<sup>9</sup> in 1932 reported in the English literature on the use of coramine in avertin narcosis. Wood<sup>10</sup> in 1933 and Levi and Krinsky<sup>11</sup> in 1936 further emphasized its value. The latter authors found, in studying the effect of coramine on postpartum patients under the influence of barbituric acid drugs, that it greatly shortened the postpartum narcosis period and that patients in extremis after administration of nembutal and paraldehyde recovered after treatment with coramine. Schube,<sup>12</sup> studying the effects of coramine on patients in a mental institution who had received over-doses of phenobarbital, found it effective as a life saving analeptic (1936). P. G. Fratten<sup>13</sup> noted in 1940 that coramine appeared to be the best drug in the prevention and therapy of complications of intravenous barbiturate narcosis. Harris et al.,<sup>14</sup> reporting recently, used coramine in a case in which a young woman had taken 125 grains (8.1 gm.) of phenobarbital resulting in four days of coma. Picrotoxin seemed ineffective and "coramine was then administered intravenously when a fatal termination seemed inevitable." Improvement was steady and the patient recovered.

Coramine (Nikethamide) is a quick acting analeptic, vasopressor and respiratory stimulant. Its action is primarily on the higher brain centers although all portions of the cerebrospinal axis, respiratory, vasomotor and vagal centers of the medulla, and the cerebral cortex are affected. It thus helps to restore normal vascular tone, increase cardiac efficiency, deepen respiration and combat anoxemia. Frequently repeated doses of coramine as used, are not cumulative in producing convulsions; on the other hand picrotoxin, repeatedly administered, tends to cause convulsions which can be combated only by further administration of barbiturates. Androp<sup>15</sup> feels that picrotoxin is contraindicated where large doses are needed for therapy because of the danger of convulsions. Freireich and Landsberg<sup>16</sup> have described unsatisfactory experiences with picrotoxin in the treatment of acute barbiturate poisoning, mainly because of the production of convulsions.

#### METHOD OF TREATMENT

A standard method of treatment of barbiturate poisoning was established and followed in all cases in the Queens General Hospital. This consisted of certain preliminary procedures common to all groups, the only variation in the treatment being the choice of coramine or picrotoxin.

##### Routine treatment:

1. A history was taken and physical examination was done, and an attempt made to identify the drug ingested. Wherever possible the prescription numbers were checked and the drug established. Members of the family were sent for to determine the amount of the drug in the patient's possession if known.

2. In all cases the stomach was aspirated with a large bore rubber tube, and washed with four to five liters of tap water, the organ being left empty. The washings were saved and sent either to our own hospital laboratory or to the Medical Examiners laboratory at Bellevue Hospital. The patients were then catheterized and the urine also sent for toxicological examination. (In all cases included in this report barbiturates were found either in the stomach contents or urine or both.)

3. An intravenous infusion of glucose and saline was started. Plasma was given to those in shock. The patient was put in a mild Trendelenberg position.

4. An airway was inserted where needed.

5. Bronchoscopy was done immediately wherever aspiration of food was suspected.

6. Frequent aspirations of the nasopharynx were done in comatose cases to maintain an unobstructed airway.

7. Either coramine or picrotoxin was used intravenously, using the infusion tubing as a ready means of entrance.

8. Nasal oxygen was used if need seemed evident.

9. Chemotherapy: Penicillin was employed, 50,000 units every three hours, intramuscularly, if temperature rose.

10. If the comatose condition persisted for several days, the nitrogen balance was considered and intravenous aminoacids, 70 gm. a day, were given. Vitamin therapy, thiamin chloride 5 mg., riboflavin 5 mg., nicotinic acid 50 mg., and vitamin C 100 mg. were given three times a day.

11. Nursing care is of great importance, with particular reference to turning the patient as a continual stimulant, to oral hygiene, to padding pressure points, to reduction of fever and to protecting against bullae.

#### CORAMINE THERAPY

1. Routine procedure previously listed.

2. Five c.c. of 25 per cent coramine (10 c.c. in our latest cases) was given intravenously, followed by 5 c.c. every five minutes for the first hour. In addition, a constant amount was given by intravenous drip so that a base line amount of 5 c.c. per hour was administered. After the first hour, booster doses of 5 c.c. intravenously were given, on the hour. (This is important as the patients tend to relapse otherwise.) In more severe cases 5 c.c. were given every half hour by the clock, as boosters.

3. Therapy was continued until the patient had a return of reflexes, and moved spontaneously. (We now feel that this should be continued to the point of responding to stimuli such as answering questions, etc.)

#### PICROTOXIN

1. A test dose of 3 mg. was given intravenously. If there was no reaction, 3 mg. was repeated every five minutes for three doses. After a 15

minute interval another series of three injections at five minute intervals was carried out. Therapy was continued thus until the return of reflexes and spontaneous motion. The patient was watched closely for dilating pupils and carried just to the point of muscle twitching. Sodium amytal was at hand in case of convulsions. In cases where coma was not deep a smaller dose was used as a follow-up with 3 mg. every 15 minutes.

### MIXED (CORAMINE PLUS PICROTOXIN)

This consisted of the usual coramine routine plus a booster dose of picrotoxin, 3 mg. every 15 minutes.

These schedules were adhered to as closely as circumstances would allow.

### GRADING OF CASES

All cases were graded as to severity in four groups in accordance with the criteria shown in table 1.

No case listed as grade 1 to 3 died regardless of the treatment, picrotoxin or coramine.

TABLE I

Grade	Conscious	Tendon Reflex	Corneal Reflex	Swallowing Reflex	Pupils	Coma
1	Yes	Yes	Yes	Yes	Normal	No
2	Semi	Yes	Yes	Yes	Constric.	No
3	No	Absent	Yes	Absent	Pinpoint	Yes
4	No	Absent	Absent*	Absent	Pinpoint	Deep

\* The most important differential of a grade 3 from a grade 4 is the loss of the corneal reflex. This was found to be a sign of a poor prognosis.

A summary of the data in table 2 is given in table 3.

The extenuating circumstances should be considered in evaluating the above data, particularly the cases listed that entered the hospital in extremely serious condition and survived only a few hours. Examples: In 1945 list, Case 17, age 90; 1946 list, Cases 6 and 14, each in the hospital less than a day; also Case 7 (1946) with digestion of the bronchial tree and pneumonia.

Also note that one grade 4 case (No. 2, 1945 list) took only nine grains of a barbiturate, was treated with picrotoxin, and this drug was given credit for the successful result.

### CASE REPORTS

*Case 1* (No. 3, 1945 list): This 55 year old white female was admitted an indefinite length of time after having ingested a large number of capsules of seconal. Physical examination on admission revealed a deeply comatose patient breathing slowly and quietly. The pupils were constricted and the eyes were slowly wandering. Corneal reflexes were absent. The chest showed moist rhonchi bilaterally. Heart and abdomen were normal. No abdominal reflexes were present. The extremities

were flaccid. All reflexes including biceps, triceps, patellar and ankle reflexes were absent. The patient was considered a grade 4 case. Urine was positive for barbiturate in large amount.

The usual supportive routine was given and picrotoxin was started. After 84 mg. of picrotoxin the patient had shown little response. The reflexes were still absent and the patient was still of grade 4 severity. Seven hours from the time of admission coramine was started and the patient showed a good reaction at once. The respirations increased, the reflexes returned, and after the administration of 21 c.c. of coramine, the patient was moving spontaneously. She went on to an uneventful recovery.

In this case we felt that picrotoxin was not improving the patient's condition and that only after the use of coramine was there a decided clinical improvement.

*Case 2* (No. 18, 1945 list): This 43 year old white male was admitted after having taken an unknown amount of one of the barbiturates. He was deeply comatose on admission with complete areflexia, including absent corneal reflex. The pupils were small and a wandering motion of the eyes was present. The heart and chest were normal. The patient was considered a grade 4 case.

The routine supportive measures were carried out. Coramine was started. After 5 c.c. of coramine the patient reacted strongly with coughing, attempted vomiting,

TABLE II\*

1945 Cases

No.	Age	Days in Hosp.	Dose Grains	Grade	Total Treatment	Response	Complication
1	28	6	18 N	2	6 mg. Pic.	Good	
2	63	6	9	4	42 Pic.	Good	
3	55	10	? Sec.	4	84 P, 21 c.c. C.	Fair	Slow
4	31	2	13½ Pent.	2	0	Good	
5	73	7	?	3	45 P.	Good	
6	25	6	?	3	24 P.	Good	
7	30	4	37 Ph.	2	2 C.	Good	
8	51	4	?	2	15 C.	Good	
9	46	2	18	3	120 P.	Fair	Convulsions
10	53	11	?	2	16 P.	Good	
11	30	2	12	2	15 P. 8 C.,	Good	
12	18	3	27 N.	2	15 P.	Good	
13	18	1	20 N.	2	0	Good	To psycho. hosp.
14	68	2	?	3	42 C., 12 P.	Good	
15	15	1	7½	1	0	Good	
16	29	3	70	2	0	Good	
17	90	1	Large	4	24 P., 50 C.	Death	Death
18	43	6	?	4	5 C.	Good	
19	12	1	12	2	22 C.	Good	
20	56	2	19 Sec.	2	18 P., 16 C.	Good	
21	26	6	?	1	0	Good	
22	40	3	?	2	6 P.	Good	
23	32	3	30 N.	2	3 P.	Good	
24	76	7	? N.	3	87 P.	Good	
25	37	2	12	2	0	Good	
26	28	1	25	2	0	Good	

\* Code:

Pent.—Pentobarbital  
 N. —Nembutal  
 Sec. —Seconal  
 Ph. —Phenobarbital  
 O. —Supportive therapy only  
 Picrotoxin in mg.  
 Coramine in c.c.

TABLE II—*Continued*  
1946 Cases

No.	Age	Days in Hosp.	Dose Grains	Grade	Total Treatment	Response	Complication
1	45	3	23	2	45 C.	Good	To psycho. hosp.
2	38	4	?	4	17 C., 15 P.	Residual	
3	27	3	12	1	0	Good	
4	32	14	36	3	188 C.	Good	Death (aspiration pneumonia)
5	30	3	Large	4	151 C., 26 P.	Death	
6	50	1	Large	4	6 C.	Death	
7	41	3	Large	4	141 C., 30 P.	Death	Death (in hosp. 3 hrs.)
8	18	5	42	3	75 C.	Good	
9	53	4	Large	3	12 C.	Good	
10	42	12	?	2	52 C.	Good	Extensive aspiration bronchopn.
11	27	1	?	2	0	Good	
12	52	1	24	2	30 gr. Caf.	Good	
13	46	1	23	3	11 C.	Good	
14	48	1	45 N.	4	109 C.	Death	
15	36	1	43	2	3 C.	Good	
16	34	1	8	2	0	Good	
17	23	1	18	2	0	Good	
18	43	1	30	3	28 C.	Good	
19	69	1	8	2	12 C., 4 P.	Good	
20	35	1	12½	1	5 C.	Good	
21	38	1	?	2	11 C.	Good	
22	35	1	12	1	0	Good	
23	42	1	75	2	5 C.	Good	
24	32	1	30	2	3 C.	Good	
25	31	2	20	3	15 P.	Good	
26	15	1	7½	2	3 C.	Good	
27	50	1	26	1	0	Good	
28	30	1	4	1	0	Good	
29	50	2	27 N.	2	0	Good	
30	23	1	3	1	0	Good	
31	15	1	5	1	0	Good	
32	47	2	45 N.	4	137 C.	Death	

TABLE III

Grade	No. Cases	Treatment				Deaths	Deaths in Treatment Groups			
		Pic.	Cor.	Mix	Routine No Drug		Pic.	Cor.	Mix	Routine
1	9	0	1	0	8	0				
2	28	5	10	3	10	0				
3	11	5	5	1	0	0				
4	10	1	5	4	0	6	0	4	2	0
	58	11	21	8	18	6				

dilating pupils and spontaneous motions. No further coramine was given and the patient went on to recovery although he was somewhat drowsy for 24 hours.

Note: This was one of the best results with a small dose of coramine and illustrates the markedly individual character of the response. Large amounts of barbiturates were recovered from the gastric washings and urine. At times there seemed

TABLE IV

Year	Cases	Deaths
1941	6	0
1942	15	2
1943	9	1
1944	11	0
1945	26	1
1946	32	5
	<hr/> 99	<hr/> 9 = 9.1%

to be no correlation between the grade of narcosis and the rapidity of the response to the analeptic.

*Case 3* (No. 1, 1946 list): This 45 year old white male was admitted in a comatose state after having ingested 23 grains of seconal. He was assessed as a grade 3 case with peripheral reflexes absent but corneal reflexes present. The usual routine was followed plus coramine. The patient was conscious in two hours with a marked response to the initial dose of 10 c.c. of coramine. Only 22 c.c. in all were used.

*Case 4* (No. 5, 1946 list): D. A., a 30 year old white female, was admitted in a comatose condition, at 10:00 p.m. on March 23. She had told friends a short time previously that she had taken a large number of nembutal capsules. Her stomach was promptly lavaged at another hospital and she was brought to the Queens General Hospital for treatment.

When first seen in the admitting department approximately 70 minutes after she had taken the barbiturate, and 20 minutes after completion of a gastric lavage she presented a picture of a deeply comatose patient with complete areflexia including absent corneal reflexes (grade 4). Blood pressure was 80 mm. Hg systolic and 0 mm. diastolic, pulse rate was 100, respirations were 24, and temperature was 99° F. The chest showed rhonchi, no dullness; heart sounds were good.

Picrotoxin treatment was instituted with the dosage and procedure outlined. The condition during the night changed but little except for occasional muscular twitching; the respirations became 35 a minute. Oxygen was given. At 3 a.m. corneal reflexes and tendon reflexes had returned, but by 8 a.m. they were absent again in spite of steady administration of picrotoxin. That evening (20 hours after treatment was begun) pulmonary edema was noted with full neck veins and rapid pulse. The knee jerks were slightly positive, the eyes wandering; some reaction was noted to the suction catheter in the pharynx. The temperature had risen to 102° F. White blood count was 40,200, 82 per cent polymorphonuclears; red blood count was 5.1 millions; hemoglobin was 14.5 gm. The CO<sub>2</sub> combining power was 46 vol. per cent, urea nitrogen 47 mg. per cent, creatinine 2.6 mg./100 c.c. Penicillin, 30,000 units every three hours, was begun intramuscularly.

On the morning of March 25 her condition was approximately the same and coramine was begun, the picrotoxin being continued. In four hours there seemed to be a change for the better; she now moved her head and her lips, her reflexes had returned, the pupils were small; she was vomiting yellow fluid. That evening the temperature rose to 103.5° F., and at 1 a.m. she suddenly became worse. Her face was brownish, respirations were rapid, pulse rate was 190, heart sounds were fair, restlessness was pronounced, pupils were dilated and divergent.

At 9 a.m., March 26, 1946, she was suffering from peripheral vascular collapse. Blood pressure was 0/0, skin was pale and moist, respirations were shallow and gasping, pupils were widely dilated, heart was rapid, and sounds were of poor quality. Chest showed dullness in the right lower lobe. The reflexes were active. There was a sudden cessation of breathing with the heart beating five minutes longer.

This grade 4 case shows combined therapy with fatal result, death being due to pneumonia. An autopsy revealed patchy bronchopneumonia plus moderate cerebral edema.

*Case 5* (No. 6, 1946 list): A 50 year old white female was admitted approximately 12 hours after she took an unknown amount of barbiturate. Her past history was irrelevant except for a diagnosis of pernicious anemia with no therapy for months.

She was considered a grade 4 case. The temperature was 101° F., pulse 130, respirations 32, blood pressure 90 mm. Hg systolic and 50 mm. diastolic, skin of yellowish tint. The chest showed many moist bubbling râles; heart sounds were faint. The liver was two fingers'-breadth below the costal margin and a question of liver nodules was raised. Spinal tap showed pressure 230 mm. of water, with normal dynamics. Blood chemistry: blood sugar 18 mg./100 c.c., CO<sub>2</sub> 58 vol. per cent. Urine: albumin 2 +; large amounts of barbiturate were found. Blood smear was typical of pernicious anemia. Roentgenogram: The right and left upper lobes suggestive of pneumonia with atelectasis.

The diagnosis was not considered barbiturate poisoning for several hours after admission to the hospital and as a result treatment was delayed. The patient died three hours after admission.

The therapy was both late and insufficient. At necropsy, the death was considered to be due to pneumonia and pernicious anemia. This case was listed as a coramine failure, although obviously her condition was terminal on admission.

*Case 6* (No. 7, 1946 list): R. M., 41 year old white male, was admitted to the hospital February 13, 1946 in a deeply comatose state, after having been found unconscious on the floor with red and blue capsules nearby (thought to be Tuinal).

Areflexia, marked cyanosis, shallow respirations, fixed small pupils were found on examination, and the patient was vomiting. Dullness to percussion was found in the right middle and lower lobes of the lungs with absent breath sounds over these areas. The heart sounds were rapid and of poor quality. The case was considered of grade 4 severity.

Bronchoscopic aspiration shortly after admission revealed large amounts of peas and carrots, withdrawn from the pharynx and trachea. Breath sounds returned to portions of the right lung after aspiration but flatness continued at the base.

Treatment was instituted as outlined, 5 c.c. of coramine were given intravenously every five minutes, and an intratracheal catheter was passed. The condition seemed to improve with full respiration and an increase in heart sounds. After two hours of treatment, owing to an error in interpretation of orders, the dosage of coramine given was reduced to 5 c.c. every hour instead of every five minutes. A total of 28 c.c. of coramine had been given in the first two hours.

On February 14, 1946, the patient was moving about in bed, comatose, with a return of corneal reflexes only. The pulse was weak, rapid and the color of the skin cyanosed. Large amounts of brown fluid continued to be aspirated from the tracheal tube. Blood pressure was 0/0. A Levine tube was in the stomach with continual suction; an airway was in place. Roentgenogram of the lungs showed extensive patchy atelectasis and bronchopneumonia. Bronchoscopic examination revealed tarry material beyond the reach of the bronchoscope. During the afternoon, the reflexes became hyperactive and the pupils dilated. The patient was unconscious. A total of 28 c.c. of coramine was given in this 24 hour period.

On February 15, 1946 the patient's condition was poor, with temperature about 102° F.; the total serum protein was 4.2 gm./100 c.c., urine was normal, leukocytes numbered 5,500 with 72 per cent polymorphonuclears, 14 gm. of hemoglobin, and 5.7 million red blood cells. Picrotoxin, 7.5 mg., was given intravenously this day without response. The next day the temperature was higher and a return was made to coramine therapy, 3 c.c. every hour intravenously. Booster doses of 10 to 15 c.c. were given several times during the day. Although the semicoma continued, the patient moved spontaneously. Penicillin, 25,000 units every three hours intramuscularly, together with thiamine chloride and niacin, was administered. The con-



dition became worse and the patient died four days after admission, with a temperature of 103° F. rectally.

At necropsy the findings were essentially those of necrosis of the entire tracheobronchial tree with digestion of the mucosa. The lungs showed grayish-green necrosis with small abscess formation in the right middle and lower lobes, and the left lower lobe. The pathologist's diagnosis included digestion of the bronchial tree and pneumonia as the causes of death.

This illustrates a grade 4 case, treated almost entirely with coramine, only a small amount of picrotoxin being used, without recovery, death being due to pulmonary complications.

## DISCUSSION

In the years 1945 and 1946 there was a marked increase in the number of cases of barbitol poisoning and in the number of deaths, as compared with the previous three years. Some physicians maintain that most patients suffering from barbitol poisoning will eventually recover with supportive treatment and with the aid of stimulants of less potency than coramine or picrotoxin. Careful analysis of statistics proves that this is not the case. Some hastily compiled figures seem to show better results from the least strenuous treatment. This illustrates how statistics alone can mislead when taken without analysis of the background factors, particularly without grading the depth of the narcosis, aspiration, etc.

Self-medication is the main etiological factor in poisoning. In many cases, the poisoning is intended as suicide; others develop a dependence on the barbiturate and take it in too large doses. Richards<sup>17</sup> has discussed the peculiar condition known as "automatism" in which an individual having become accustomed to the use of the drugs may fail to have deep sleep develop. In this twilight zone, the individual does not exhibit normal inhibition and reason, and mechanically (automatically) takes all of the remaining tablets.

There has been a marked increase in cases of self-medication. The grade 4 group have taken enormous quantities of drugs, judging from the amount recovered in the urine and as determined by careful histories. It has been our finding that very few grade 4 cases were found in the first three years of this survey as compared with the last two years. This again simply reflects the increasing amounts of barbiturates being dispensed and therefore available. The recent attempts to class barbiturates with narcotics under the law is not the entire answer, as in all of the cases of grade 4 narcosis investigated, the drugs were obtained with a physician's prescription. Most of these people went to several doctors and obtained prescriptions from each for from 12 to 50 capsules. Some of the patients had as many as 15 bottles from as many doctors.

There has also been a swing away from the use of long acting members of the barbiturate group, such as barbitol and phenobarbitol, to the shorter and quicker acting members, notably nembutal and seconal. In our experience the latter group have been more lethal, weight for weight. Tatum<sup>3</sup>

feels that all of the barbiturates, except barbital and phenobarbital, have a short induction period.

Prolonged depression from the ingestion of these drugs results in complications of a serious nature, namely pneumonia, pulmonary edema, cerebral edema, prolonged hypoxia, nutritional deficiencies, depressed kidney function, decubitus ulcers and transient or more permanent neurological sequelae.

Analeptic treatment should be instituted as soon as possible and carried on with a definite plan adapted to needed intensity and duration. It is our feeling that where coramine has been used with unsatisfactory results in the past, in many instances better effects would have been obtained with a schedule of larger doses.

In no case where coramine failed did picrotoxin succeed in saving the patient. In several cases where picrotoxin did not help, coramine gave good results.

In several cases picrotoxin caused severe convulsions, some requiring the administration of sodium amytal for control. In no case did coramine cause convulsions. Coramine is safer to use for this reason and can be given by nurses without danger, whereas picrotoxin must be given with a physician on hand at all times because of the danger of convulsions.

Review of the statistics shows that every fatal case was in group 4. No cases listed in groups 1 to 3 died. The main difference between group 3 and group 4 is the loss of the corneal reflex. Therefore, when the corneal reflex is lost, the prognosis becomes much more grave. Sixty per cent of those with absent corneal reflex died.

The early aspiration of the stomach with immediate therapy is of prime importance. Nothing is to be lost and much is to be gained by prompt action. Even if the type of the depressant is not known, this does not change the method of treatment.

Therapy should be maintained until the patient moves spontaneously and has a return of all reflexes. It is better to continue therapy to the point of reaction, at which time the patient responds to mild stimuli.

The study and comparison of these drugs is being continued in the Queens General Hospital, this being a preliminary report. We wish to focus more attention on the value of coramine and to stress the safety of much larger doses than are usually given. Our doses are to be increased in future cases to 10 c.c. of coramine every five minutes intravenously until the patient reacts, and large doses are to be continued for some time.

#### SUMMARY AND CONCLUSIONS

The therapy of barbiturate intoxication is an increasingly important problem confronting the medical profession. Treatment is discussed comparing coramine (Nikethamide) with picrotoxin. The study suggests further recognition and use of coramine as a relatively non-toxic, effective analeptic agent in the treatment of barbiturate intoxication.

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# SKELETAL LESIONS IN HODGKIN'S DISEASE \*

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THE skeletal lesions of Hodgkin's disease are well recognized as numerous reports in the literature indicate. Steiner mentions in his Review<sup>1</sup> in 1943, having found in the Index Medicus and Quarterly Cumulative Index Medicus 1922 to 1942, approximately 92 titles of papers dealing primarily with skeletal changes. In spite of this accumulated information there are many gaps in our knowledge of the mechanism of these granulomatous lesions in the skeleton. In particular, we lack exact knowledge as to the mode of spread in the skeleton, the frequency, and the inception of the lesions, with reference to the onset of the primary disease.

It was formerly believed that Hodgkin's lymphogranuloma spread only through lymphatic tissue. At present the conception that the lesions of Hodgkin's disease may also spread through the reticuloendothelial system appears to be quite well established. Some investigators believe this disease should be considered as a disease of the reticuloendothelial system.<sup>2</sup>

There appears to be quite general agreement among investigators of Hodgkin's disease that skeletal involvement means marrow involvement. The actual mechanism of marrow involvement has not been adequately demonstrated. Three methods are commonly mentioned, direct invasion from adjoining granulomatous lesions, usually lymph nodes, hematogenous invasion through small lymphogranulomatous emboli, or transference of an agent capable of initiating a focus in situ. This latter method could also initiate a lesion primary in the bone marrow, bearing in mind, of course, that the etiology of Hodgkin's disease is at present unknown. Several authors have reported cases where the first clinical evidence of the disease was demonstrated in the skeleton.<sup>3</sup>

In the reported cases of skeletal involvement the lesions described have usually been either osteolytic (destructive) (figure 1), osteoplastic (proliferative) (figure 2) or periosteal (infiltrative) (figure 1). There are various combinations of either two or even three of the above types shown in a single skeletal lesion (figure 1).

With respect to the study of aspirated bone marrow as a means of investigating skeletal lesions in the living patient with Hodgkin's disease, it should be stated that this method is considered of little practical value by most investigators of this disease. Since 1938, we have studied the aspirated sternal marrows from 59 patients with Hodgkin's disease in order to ac-

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cumulate data, which we considered might suggest bone marrow invasion with the lesions of Hodgkin's lymphogranuloma. It was recognized that a specimen of aspirated sternal marrow would probably not contain material from an actual lesion of lymphogranuloma, except by the mere element of chance. We were searching for a cellular pattern in the aspirated specimens



FIG. 1. Combined osteolytic and periosteal lesion of femur.

of marrow that might indicate, relatively early, whether other portions of the skeletal marrow had become involved by the typical lesion of Hodgkin's granuloma. It was our hope that certain abnormal changes in the cell pattern might be demonstrated in aspirated sternal marrow from patients with Hodgkin's disease, and that these changes might be found to indicate a

functional disturbance of hematopoiesis due to granulomatous invasion of a portion of the marrow.

#### SOURCE OF MATERIAL AND METHODS

Material for this study was obtained from the hematologic clinic, the hospital and the department of pathology of the University of California Medical School. Twenty cases of Hodgkin's disease proved by autopsy were investigated for evidence of marrow involvement. The specimens of marrow studied were the usual routine specimens taken at autopsy either from the sternum or from a rib. In a few instances material was obtained from an



FIG. 2. Proliferative lesions of ilia.

actual skeletal lesion and in addition to Zenker-fixed material, spreads were made directly on glass slides and the film stained by Wright's, counterstained by Giemsa's stain. Aspirated sternal marrows were studied from 12 of these 20 patients during life. Forty-seven patients in whom the diagnosis was confirmed by surgical biopsy of an enlarged lymph node, were subjected to one or more sternal marrow aspirations in the hematologic clinic. This group of patients also had some type of roentgenologic investigation for evidence of skeletal lesions.

The technic used for study of aspirated bone marrow was the following: 1 c.c. of sternal marrow was drawn into a 5 c.c. luer syringe and immediately discharged into a centrifuge tube in which a few particles of heparin had been placed. This material was centrifuged for five minutes at approxi-

mately 2000 r.p.m. The serum and fat were withdrawn and discarded, and from the lighter colored, myeloid layer, material was transferred to a cover glass on which films were drawn by superimposing two cover glasses. After using this method for approximately one year we changed to the practice of withdrawing approximately 0.2 to 0.3 c.c. of sternal marrow into the aspirating needle and attached syringe, and transferring this material directly to the cover slips. We found our best preparations were made by withdrawing the plunger of the 5 c.c. luer syringe and attempting to pick out small pieces of marrow from the syringe by means of a capillary pipette.

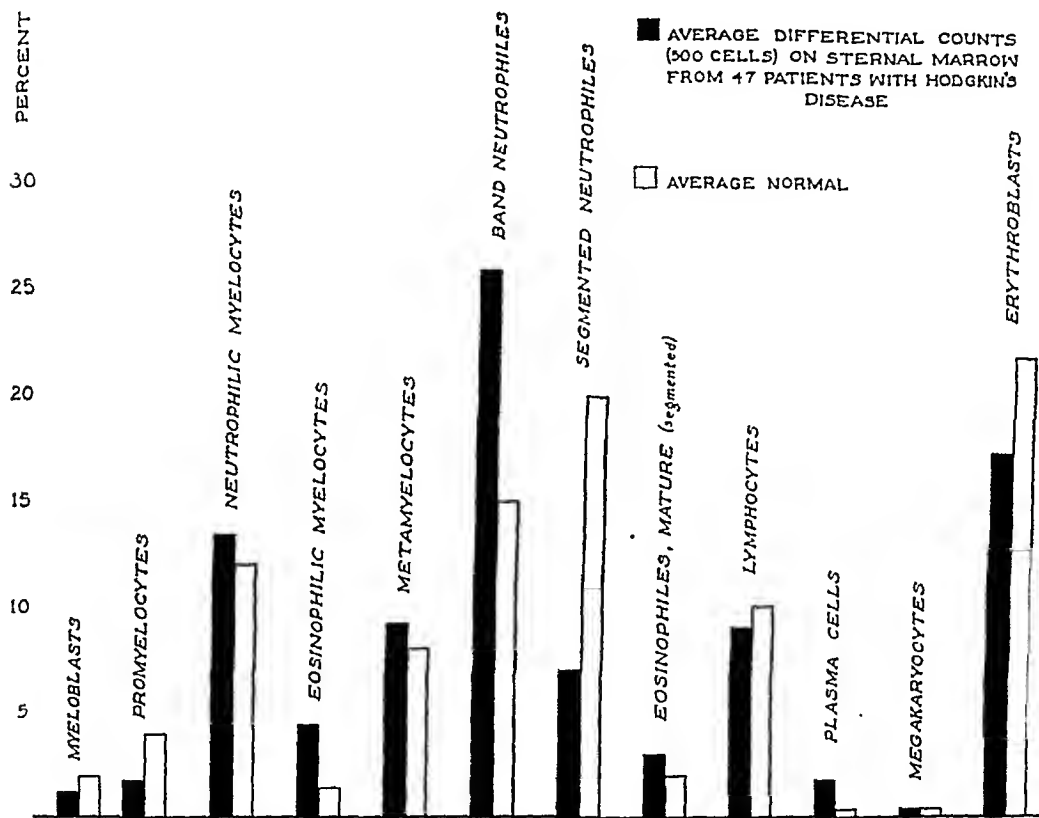


FIG. 3.

The remaining clotted portion of marrow was next removed from the syringe and placed in Zenker's solution for fixed-tissue preparations to be studied later. This method was used up until the time of completion of the present study. The marrow specimens were examined and the cells counted by both authors, each counting 500 cells.

#### RESULTS FROM ASPIRATED AND AUTOPSY MARROW INVESTIGATION

Figure 3 shows a "shift to the left" of the myelocytic elements. Of these elements the neutrophilic myelocytes showed a moderate increase, the eosinophilic myelocytes a marked increase, neutrophilic band cells dis-

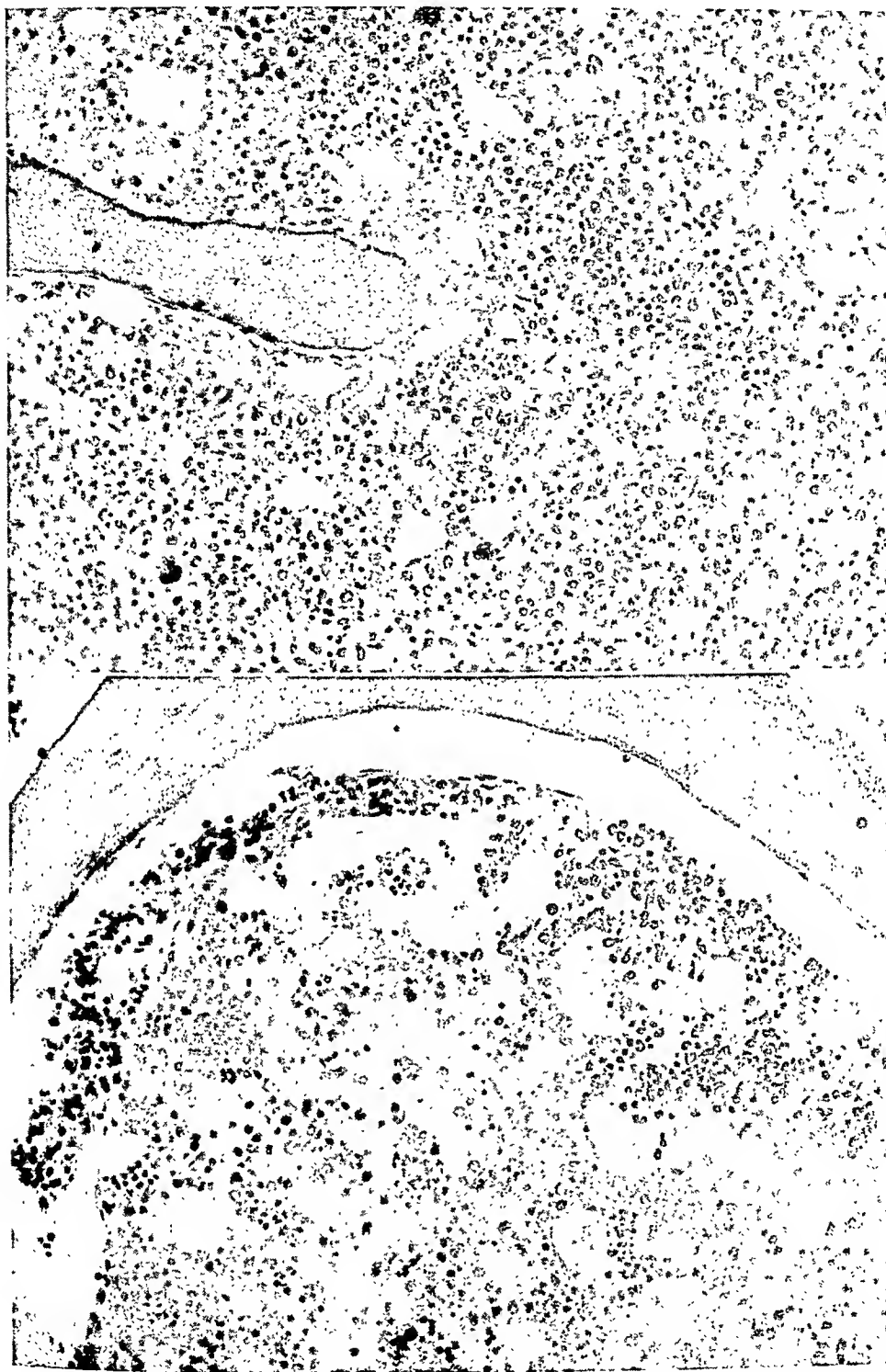


FIG. 4a (*Above*). Typical lymphogranulomatous lesion of marrow.

FIG. 4b (*Below*). Replacement of normal marrow tissue by Hodgkin's lymphogranuloma.



TABLE I

No.	Patient	Sex	Age	Clinical Manifestations	Blood Findings	Bone Marrow (Autopsy)
1	C. W.	M.	57	Chills and fever of three months' duration.	Hb. 8 gm. R.B.C. 2.5 W.B.C. 2,200	Hodgkin's granuloma
2	S. S.	M.	51	Three year history of lymphadenopathy, fever, anorexia, weakness and weight loss.	Hb. 5.5 gm. R.B.C. 2.55 W.B.C. 2,800	Hodgkin's granuloma
3	R. O.	M.	31	Obstructive jaundice. True nature of disease disclosed by operation for jaundice.	Hb. 10.4 gm. R.B.C. 3.43 W.B.C. 16,500	Myelofibrosis and eosinophilia
4	S. A. S.	M.	30	Three and one-half year history of weakness, dyspnea, abdominal discomfort. Enlarged cervical lymph nodes.	Hb. 6 gm. R.B.C. 3.1 W.B.C. 19,000	Myeloid hyperplasia
5	J. S.	F.	21	Fever, weakness, weight loss, cough and dyspnea of 15 months' duration. Enlarged nodes, left axilla.	Hb. 12 gm. R.B.C. 4.09 W.B.C. 22,800	Hodgkin's granuloma
6	C. B.	M.	42	High intermittent fever for 10 months. Generalized adenopathy. Enlarged spleen and liver. Jaundice.	Hb. 6 gm. R.B.C. 2.13 W.B.C. 1,850	Myelofibrosis with areas of pleomorphic cellularity, including many eosinophiles
7	E. E.	F.	52	Painless abdominal tumor of 10 years' duration. Enlarged thyroid. Osteolytic lesions, ribs.	Hb. 12.8 gm. R.B.C. 4.10 W.B.C. 4,800	Myeloid and megakaryocytic hyperplasia
8	P. C.	M.	36	Generalized adenopathy. Dyspnea and cough.	Hb. 12.5 gm. R.B.C. 4.44 W.B.C. 5,650	Eosinophilic hyperplasia, fibrosis, many megakaryocytes
9	W. M.	M.	27	Cervical and axillary adenopathy. Pleural effusion. Osteoplastic lesions, pelvis.	Hb. 8 gm. R.B.C. 2.73 W.B.C. 19,000	Hodgkin's granuloma
10	A. B.	M.	25	Illness of seven years' duration, manifested by fever, weakness, weight loss, abdominal pain, lymphadenopathy, splenomegaly and hepatomegaly.	Hb. 7 gm. R.B.C. 3.82	Hodgkin's granuloma
11	A. H.	F.	46	Generalized lymphadenopathy and splenomegaly.	Hb. 10 gm. R.B.C. 2.82 W.B.C. 44,250 with marked left shift.	Myeloid hyperplasia
12	J. B.	F.	18	Illness of five years' duration, severe bone pains at onset, left shoulder. Later, pains in hips, legs and back. Cervical and inguinal adenopathy one year after onset.	Hb. 3.5 gm. R.B.C. 1.00 W.B.C. 4,000	Hodgkin's granuloma

TABLE I—*Continued*

No.	Patient	Sex	Age	Clinical Manifestations	Blood Findings	Bone Marrow (Autopsy)
13	W. S.	M.	49	Lymphadenopathy, weakness, weight loss and splenomegaly. Symptoms five years' duration.	Hb. 6.9 gm. R.B.C. 3.15 W.B.C. 12,000	Hodgkin's granuloma
14	A. McD.	M.	33	Back pain and sciatic syndrome of one year's duration. Osteolytic lesions, spine.	Hb. 7 gm. R.B.C. 3.05 W.B.C. 4,000	Hodgkin's granuloma
15	J. F. L.	M.	30	Lumbar pain followed by hypesthesia of low back and paraplegia. Osteolytic lesions L3, 4. Six years' duration since onset of first symptoms.	Hb. 9.5 gm. R.B.C. 3.8 W.B.C. 4,400	Hodgkin's granuloma
16	J. L.	M.	24	Symptoms of two years' duration. Primarily those of mediastinal pressure with superior vena cava block. Pleural effusion.	Hb. 12 gm. R.B.C. 5.02	Fibrosis with eosinophilia
17	F. S.	F.	44	Dysphagia and pain in left upper quadrant for eight years. Enlarged nodes in neck. Osteolytic lesions, pelvis.	Hb. 8.8 gm. R.B.C. 2.8 W.B.C. 2,400	Hypoplastic
18	J. M.	M.	51	Intermittent abdominal pain for three months. Splenomegaly and abdominal mass.	Hb. 8 gm. R.B.C. 2.82 W.B.C. 26,500	Myeloid and megakaryocytic hyperplasia
19	W. S.	M.	27	Swelling in neck for two years and six months. Pain in right hip and low back for six months. Osteoplastic lesions, pelvis.	Hb. 7 gm. R.B.C. 2.71 W.B.C. 2,200	Hodgkin's granuloma
20	R. M. E.	F.	48	Swelling left upper quadrant five years. Pain left shoulder four weeks. Splenomegaly and hepatomegaly. Osteolytic process left humerus and scapula.	Hb. 7 gm. R.B.C. 2.75 W.B.C. 13,200	Hodgkin's sarcoma

played a marked increase, and segmented eosinophiles a moderate increase. Neutrophilic metamyelocytes were moderately increased and the plasma cells showed a well marked increase. A breakdown of these differential counts by grouping patients according to duration and distribution of their disease showed a sharp rise in per cent of myeloblasts, promyelocytes, neutrophilic and eosinophilic myelocytes, and plasma cells, in the group with longest duration, and widest distribution of disease. In at least three of these patients the marrow cell counts suggested a myelocytic leukemoid reaction. We found in those marrows where aspiration achieved satisfactory specimens, i.e., with small particles of marrow in the aspirate, a considerable

number of immature myelocytic elements with a marked increase of eosinophilic myelocytes.

Table 1 shows the results of bone marrow study of fixed-tissue preparations in 20 cases of Hodgkin's disease in whom autopsies were performed. Typical granulomatous lesions as illustrated in figures 4a, 4b, were found in the marrows of 11 patients. In four other cases the marrow disclosed the picture of a leukemic infiltration with a preponderance of neutrophilic and eosinophilic myelocytes. Table 1 discloses peripheral blood findings of a well marked leukocytosis in three of these cases; in one instance a leukocytic count of 44,200 was present. The aspirated sternal marrow in 12 of these patients was examined during life and in each instance disclosed a marked shift to the left, with a high per cent of neutrophilic and eosinophilic myelocytes.

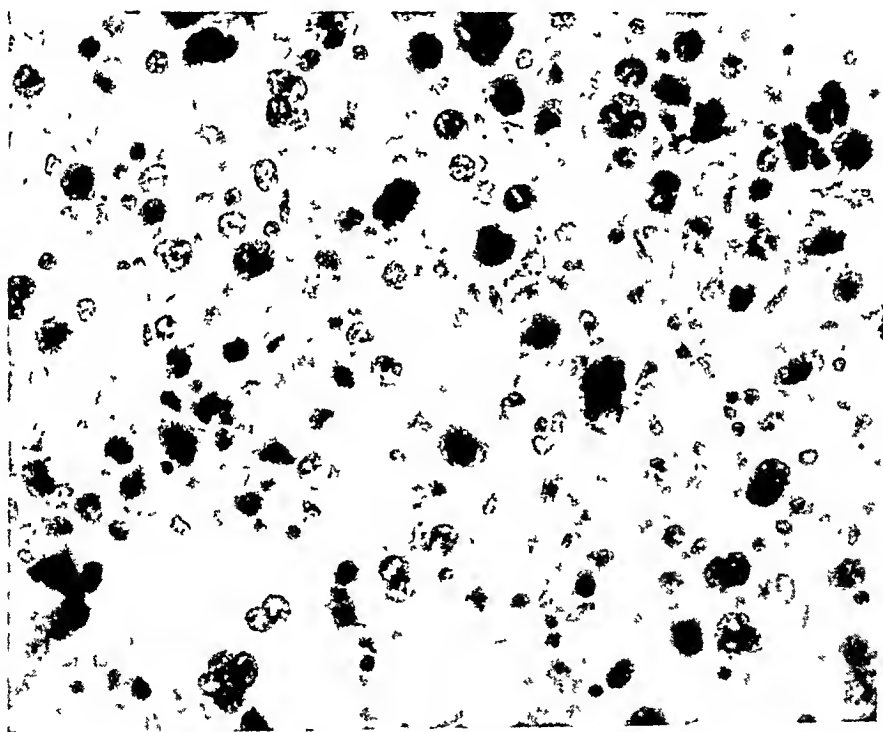


FIG. 5. Sternberg-Reed cells and megakaryocytes.

We were impressed by the large number of megakaryocytes encountered in some of the preparations (figure 5). In order to determine the significance of this observation, particularly as megakaryocytes in Hodgkin's disease have frequently been studied and commented on by other investigators, we did a series of counts on the marrows of 18 autopsy cases and 49 living patients. The method used was to count 100 fields with a high-dry lens. Normals used for control showed an average of 20 megakaryocytes per high-dry field. Forty-nine patients in various stages of Hodgkin's disease showed an average of 25.5; the fixed tissue preparations of 18 autopsy patients showed an average of 78 per 100 high dry fields. One patient whose counts

were not included showed 414 megakaryocytes per 100 high dry fields. This patient showed a marked anemia, her marrow revealing much fibrosis in addition to many megakaryocytes and areas of Hodgkin's granuloma. This patient's marrow corresponds to a type of Hodgkin's disease described by Rhoads<sup>4</sup> in connection with studies on aplastic anemia, and designated refractory anemia with megakaryocytic marrow.

### INCIDENCE OF SKELETAL LESIONS

Table 2 shows the incidence of skeletal lesions in Hodgkin's disease as determined by various investigators. Two types of investigation are recorded in the statistics of this table: namely roentgenologic and post mortem.

TABLE II

Statistics of Various Authors Showing Incidence of Skeletal Lesions in Hodgkin's Disease

Authors	Total No. of Pts.	Number with Bone Lesion	Percentage of Incidence	Method of Study
Dresser and Spencer	149	16	10.7	Roentgenologic
Vieta, Friedell and Craver	257	38	14.8	Roentgenologic
Vieta, Friedell and Craver	47	23	49.0	Necropsy
Craver and Copeland	172	27	15.7	Roentgenologic
Uehlinger	50	15	30.0	Necropsy
Stephani	70	28	40.0	Necropsy
Schenk	107	8	7.5	Roentgenologic
Werthman	12	8	66.0	Necropsy
Authors	20	11	55.0	Necropsy
Authors	65	17	26.0	Roentgenologic

A comparison of these percentages derived from the two types of study indicate that roentgenologic statistics may be misleading unless the limitations of this method of study are kept in mind. Roentgenologic bone surveys must be carried out on all patients studied and roentgenograms carefully searched for skeletal lesions in order to obtain the true statistical incidence. Critical study of postmortem marrow investigations reveals a similar type of statistical error. This point is well illustrated by the postmortem studies of Steiner in 1943.<sup>1</sup> He secured specimens from different portions of the skeleton (three to nine bones) in 14 consecutive cases of Hodgkin's disease; marrow sections from 62 bones disclosed granulomatous lesions in 38 of 62 sections or a per cent of 61.2. In three cases examined every section showed the presence of Hodgkin's lymphogranuloma. In each of three cases which showed no involvement, only three different bones were examined. It is quite apparent that more extensive and particularly more carefully planned studies in connection with both types of investigation will reveal a higher incidence of skeletal involvement than the figures recorded up to the present.

### ORIGIN AND SPREAD OF MARROW LESIONS

Skeletal lesions are practically synonymous with marrow lesions; the focus originating in the bone marrow and enlarging until it erodes the con-

tiguous cortex of the bone. Occasionally instances are encountered where the granuloma appears to invade the bone from without, entering through the periosteum from contiguous lymphogranulomatous tissue. It is our impression that when this occurs the disease is widespread and fairly well advanced. Our interest has centered on the question of how early in the course of the disease does bone marrow involvement occur? A fairly large number of our cases appeared to have marrow involvement relatively early in the course of their disease. One method of obtaining direct proof of this possible involvement would be multiple samplings of the red marrow sites in the skeleton by means of surgical biopsy. This is scarcely feasible in the living patient so that it becomes necessary to use indirect methods such as study of aspirated marrow specimens.

It seems reasonable to assume that the marrow and the spleen because of their histological structure may be quite as favorable sites for early proliferation of Hodgkin's lymphogranuloma as lymph nodes. Both marrow and splenic tissue have labile growth potentialities in their cellular components, and their filter propensities with stasis of blood in the sinusoids, might readily harbor the agent responsible for proliferation of lymphogranulomatous lesions. This idea might well be objected to on the ground of its being purely theoretical, yet it constitutes an approach to the study of the spread of marrow lesions, albeit not an easy approach. There are lesions described in the literature<sup>5</sup> where the spleen and bone marrow have been involved with Hodgkin's granuloma before recognizable involvement of lymph nodes has occurred. Two patients of our series are herewith briefly reported as illustrating this point.

*Case 1*, an Italian girl, aged 14, became ill in March, 1937, with pain over the left scapular region. Pain was severe enough to interfere with sleep. About two months after onset, the pain shifted to the right knee, then after one month it involved the left knee as well. Pain interfered somewhat with walking, but the knee-joints proper were not swollen nor sore. In December, 1937, she had to stop school because of pain over both lower quadrants of the abdomen and over the low back. After a few weeks pain extended to involve the left hip and she walked with a limp. In January, 1938, a few tender "lumps" appeared in the left side of the neck. During January and February, 1938, patient remained in bed. During this time a "dribbling" of urine appeared. By April of 1938 the patient was having difficulty in sitting upright in bed; she was scarcely able to walk, so on April 29, 1938, she was admitted to the University of California Hospital. The pertinent findings at this time were: A few slightly enlarged palpable lymph nodes in the posterior triangles of the neck. Blood count, hemoglobin 70 per cent; red blood cells 3.70 millions; white blood cells 16,900; neutrophils 84; filaments 39; non-filaments 45; lymphocytes 15; monocytes 1 per cent; blood serum calcium 11.8 mg. per cent; phosphorus 6.1 mg. per cent. Biopsy of a cervical lymph node was reported; lymphoma, probably Hodgkin's disease. Roentgenograms showed: osteolytic lesions in the distal extremities of both femora (figure 6), proximal ends of both tibiae and fibulae, collapse of ninth thoracic vertebra (figure 7), involvement of both wings of the ilia with areas in both ischia (figure 8) and head of left humerus. The patient was started on roentgen therapy with some improvement but as the diagnosis of Hodgkin's disease was questioned by the roentgenologist administering the treatment, a surgical biopsy of the right iliac crest was

performed. The fixed tissue marrow specimens were diagnosed as Hodgkin's disease. Roentgen therapy was continued; also a limited course of therapy with the radioactive isotopes of strontium and phosphorus was administered. After entry into the hospital her anemia became progressive, necessitating multiple transfusions. In De-



FIG. 6. Case 1. Osteolytic lesion distal portion femur.

cember, 1940, the skull showed osteolytic lesions by roentgenologic examination. On September 7, 1941, she entered the hospital for further transfusions. By this time her anemia was extreme, the hemoglobin was 18 per cent; red blood cells 900 thousand;

white blood cells 4,000, neutrophils 61; filaments 35, non-filaments 26; lymphocytes 26; monocytes 13. After five transfusions she recovered sufficiently to leave the hospital, returning on April 29, 1942, at which time death occurred, exactly four years after her first hospital entry and five years after her first symptoms were noted. At necropsy the marrow was found to be extensively invaded and crowded out by lymphogranulomatous lesions with areas of new marrow formation in the fatty portions of the long bones. The history indicates that the first involvement of superficial



FIG 7. Case 1. Collapse of ninth thoracic vertebra.

lymph nodes was noted 10 months after symptoms of skeletal involvement appeared.

*Case 2.* A single female, aged 44, was referred to one of the authors (E. H. F.), March 11, 1947, because of severe anemia which did not respond to therapy with either parenteral liver extract, folic acid or iron by mouth. Examination revealed a pale, slightly icteric woman with a very large spleen which extended well into the pelvis. Laboratory studies indicated a severe hemolytic anemia, and splenectomy was advised. On March 20, 1947, Dr. Frederick Foote removed the patient's spleen at the Franklin

Hospital. At operation four nodules about 2.5 cm. in diameter were noted in the tissues of the splenic pedicle. One of these nodules was pale yellow in color and firm in consistency, while the other three were bluish in color, resembling splenic tissue. The yellowish nodule was removed and a frozen section prepared for emergency diagnosis, which was reported as typical of Hodgkin's disease. The spleen along with the three accessory nodules was removed. Exploration of the abdomen failed to reveal any other nodes or evidences of spread of Hodgkin's lymphogranuloma. The spleen weighed approximately 1500 grams and a section showed whitish yellow nodules varying from a millimeter to about 2 cm. in diameter. Fixed tissue sections of the spleen showed microscopically the lesion of Hodgkin's disease. The patient made an uneventful recovery from her operation, and with the aid of transfusions (6 liters of blood) the blood count slowly returned to normal after approximately three months in the hospital.



FIG. 8. Case 1. Lesions of ilia and ischia.

After about three months spent at home, during which time she was comfortable and felt quite well, pain appeared over the lower spine. Patient's home was some distance from San Francisco; therefore she had been requested to return to the hospital in the event of symptoms recurring. On October 7, 1947, at reentry, a chest film and roentgenograms of the spine were made. These were negative with the exception of increased density in the fourth lumbar vertebra. Roentgen therapy was given over the spine with relief of pain after six treatments. On November 11, 1947, approximately one month later, the patient returned, complaining of pain over the thoracic spine and left chest. Roentgenograms of the spine now showed a compression fracture of the twelfth thoracic spine (figure 9). On November 26, 1947, a bone survey showed a destructive lesion at the medial end of the left clavicle (figure 10), also an





FIG. 9. Case 2. Compression fracture twelfth thoracic vertebra.



FIG. 10. Case 2. Destructive lesion medial end left clavicle.

osteolytic lesion of the ascending ramus of the right ischium and a portion of the acetabulum. Roentgen therapy was carried out in an attempt to alleviate pain and prevent the spread of her lymphogranulomatous lesions. On January 29, 1948, films showed new destructive lesions involving the fifth and sixth thoracic vertebrae and the second right rib at the axillary line. On March 11, 1948, films disclosed osteolytic lesions throughout the shaft of the middle portion of the left femur (figure 11). The bones of the pelvis were now intact following roentgen therapy. By April 8, 1948 further roentgenograms showed compression fractures of the first and second lumbar

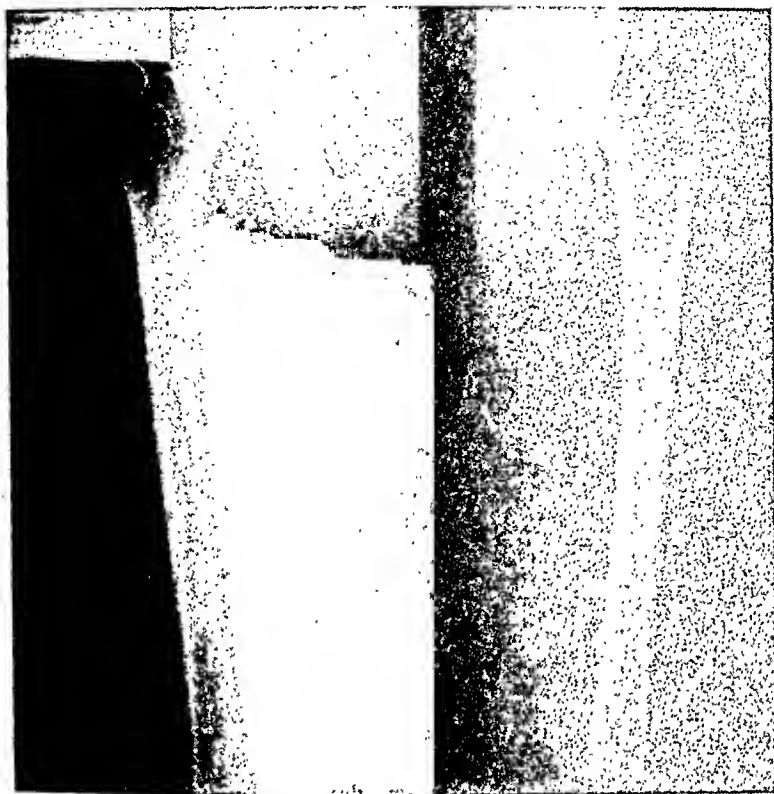


FIG. 11. Case 2. Osteolytic lesions middle portion left femur.

vertebrae, healed, recalcified fractures of the second and fifth right ribs and recent spontaneous fractures of the tenth and eleventh ribs, left, in the anterior axillary line.

A notation in the patient's record states that on December 15, 1947, she noted enlarging lymph nodes on the right side of the neck in the anterior and posterior cervical triangles. This was approximately 10 months after our first examination. The appearance of enlarging superficial lymph nodes was carefully watched for and checked, as we were anxious to ascertain the time relation of the first definite evidence of lymph node involvement in relation to the onset of skeletal lesions. On November 11, 1947 there was roentgenologic evidence of skeletal involvement in rather widely separated portions of the skeleton. It will be noted that the clavicle was involved on the opposite side from the cervical lymph node involvement. The patient is still under treatment and no evident lymph node involvement has occurred on the left side of the neck.

### DISCUSSION

Figure 3 yields data which we have interpreted as indicating widespread irritation of the bone marrow due to focal lesions of Hodgkin's lymphogranuloma. Whether these focal granulomatous lesions are due to metastases from lesions outside the marrow or arise in situ from the agent responsible for the lesions of Hodgkin's disease is not clear at the present time.

In 1924 Symmers<sup>6</sup> reported, "The bone marrow in Hodgkin's disease may react in at least two different ways: (a) it may show hyperplastic changes, particularly in the eosinophiles, and eosinophilic myelocytes; or (b) it may be replaced by tissue of identical composition with that of the diseased

lymph nodes, sometimes over an extraordinarily wide distribution." During,<sup>7</sup> in 1918, stated that while eosinophiles are not peculiar to Hodgkin's disease, there is no other condition in which they are found in such large numbers. Montgomery<sup>5</sup> (1928) concludes from his study "that marked eosinophilia in the tissue sections in Hodgkin's disease points to an essential irritation and involvement of the bone marrow in this disease and should lead to a careful examination of the osseous system in such cases."

These quotations are from authors reporting studies in Hodgkin's disease before marrow aspiration was in use as a practical method of marrow study. Their conclusions assume added significance when confirmed by the simple methods of marrow study available today and reported in detail in our present study.

### SUMMARY OF RESULTS

1. A cellular pattern, uniform in type, was demonstrated in the aspirated marrows of 59 patients with Hodgkin's disease. This pattern showed an increase of the myelocytic elements (a shift to the left) with emphasis on the neutrophilic and eosinophilic myelocytes, the band neutrophiles, eosinophilic segmented cells and the plasmacytes.

2. This same cellular pattern was present in the aspirated sternal marrow of 12 patients, 10 of whom showed Hodgkin's lymphogranuloma in the marrow at autopsy.

3. The marrows of 67 patients, including 18 autopsy cases, showed an increase of megakaryocytes, when enumerated by a special technic with an established normal. This increase of megakaryocytes we interpret as indicative of marrow irritation and possible degenerative cellular changes.

4. We believe the incidence of skeletal lesions shown by roentgenologic examination is necessarily incomplete and too low, as marrows with Hodgkin's lymphogranuloma may contain lesions too small to involve the adjacent cortical portion of the bone.

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# INTRAVENOUS NEOSTIGMINE IN DIAGNOSIS OF MYASTHENIA GRAVIS \*

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THE diagnosis of myasthenia gravis has been made with ever increasing frequency since 1935 when Walker<sup>1</sup> demonstrated the remarkable therapeutic effect of neostigmine and Viets and Schwab<sup>2</sup> described its diagnostic use.

Prior to 1942 there were only four cases on our records. In the past five years 23 more have been diagnosed. These cases will be reported later. The purpose of this paper is to present a modification of the neostigmine diagnostic test described by Schwab and Viets.<sup>3</sup> Their test consists of the intramuscular injection of 1.5 mg. of neostigmine methylsulfate combined with 0.6 mg. of atropine sulfate in a single "diagnostic" ampule. The injection is followed by an hour of observation at 10 minute intervals "scoring" the patient on both the subjective and objective improvement.

In our experience with this test, the initial response began in 15 to 30 minutes and maximal improvement was unpredictable often coming an hour or more after injection. It seemed possible that intravenous neostigmine might give a more prompt and complete response.

A thorough study of neostigmine toxicity was reported by Aeschlimann and Reinert<sup>4</sup> in 1931. They found that the dose of neostigmine causing 50 per cent mortality in mice was 12 to 16 mg. per kg. orally, 1 mg. per kg. subcutaneously and 0.45 mg. per kg. intravenously.

No fatalities attributable to neostigmine were found in the literature up to 1942.† A personal experience by Goodman<sup>5</sup> was reported in 1937. He took 45 mg. of neostigmine bromide by mouth and had an unpleasant, apparently parasympathetic, reaction terminated by atropine.

No reported clinical experience with intravenous neostigmine could be found up to 1942. Since that time, however, Bennett and Cash<sup>6</sup> have advised rapid intravenous neostigmine to offset the curare effect in their diagnostic test (1943). Viets,<sup>9</sup> in 1944, reported the administration of neostigmine by slow intravenous drip to a seriously ill myasthenic.

It seemed to us that the promise of a better diagnostic test offset what appeared to be a minimal risk. As neostigmine is apparently twice as toxic

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The author expresses his appreciation to the Hoffmann-La Roche Company for generously furnishing most of the neostigmine ("Prostigmin") used in this series.

† Addendum: Since the writing of this paper, a fatality, presumably due to the intramuscular injection of 1 c.c. (0.5 mg.) of neostigmine, has been reported.<sup>12</sup> That this was probably an example of unusual individual susceptibility was mentioned by Dr. Merrill and further stressed by me in a letter to the Editor of the *Journal of the American Medical Association*.<sup>13</sup> In this letter immediate use of atropine, intramuscularly or intravenously, for any untoward reaction to neostigmine was reemphasized.

intravenously it was decided that only one third the intramuscular dose should be used. Accordingly, on June 8, 1942, 0.5 mg. (1 c.c. of 1/2000 solution) of neostigmine methylsulfate was given intravenously to an 18 year old girl complaining of ptosis, diplopia, dysarthria, dysphagia and general incapacitating muscular weakness of four years' duration. Within 15 seconds she said distinctly, "I don't see double anymore." Within two minutes her ptosis and myasthenic facies had disappeared completely and she demonstrated normal muscle power and swallowing ability. There were no untoward reactions to the drug.

### THE INTRAVENOUS TEST

A thorough history is taken with special emphasis on ptosis, diplopia, dysarthria, dysphagia and general muscular weakness variable with rest and fatigue, menstruation, pregnancy, acute infections and emotional upsets.

On examination one should study the degree of ptosis, limitation of extra-ocular movements, ability to smile, whistle, distend the cheeks, chew gum, swallow liquids, count to 100, maintain grips, lift, walk and step up on a chair or stool. Each of these performance tests should be repeated sufficiently to detect abnormal fatigability. The results should be carefully recorded.

If the history and physical findings are sufficiently characteristic of myasthenia gravis, 1 c.c. of a 1/2000 solution (0.5 mg.) is injected intravenously within a timed 1 minute period. Improvement in a true case of myasthenia gravis often begins before the needle can be withdrawn and is usually maximal in at most five minutes (figures 1 and 2). Therefore, the performance tests should be repeated after five minutes have elapsed and the degree of objective improvement recorded. Subjective improvement is not considered, thus lessening the possibility that a psychic response to an injection might result in a false positive diagnosis. Occasionally, in very mild true myasthenia gravis the response to an intravenous dose of 0.5 mg. of neostigmine is doubtful or minimal. In such an instance the test should be repeated on the following day with 1 mg. provided there were no untoward reactions to the 0.5 mg. dosage.

Atropine sulfate, usually 0.6 mg., should always be kept at hand and should be injected subcutaneously whenever side-effects become manifest, but is never to be injected with the neostigmine. Viets<sup>10</sup> has stated that marked side-effects from neostigmine almost disprove a diagnosis of myasthenia gravis, and our experience has been similar. However, these side-effects, although uncomfortable, are apparently not dangerous and we do not, as Viets advises, use atropine simultaneously with neostigmine to offset them. We feel that these reactions, however uncomfortable, are highly valuable diagnostically.

In the past five years we have given neostigmine intravenously on several hundred occasions, not only as a diagnostic test for myasthenia gravis but also to arthritics and neuro-muscular cases. The only side-effects worthy

of note were encountered in non-myasthenic individuals and in those with extremely mild myasthenia gravis. These consisted of mild abdominal cramping, muscle fibrillations, flushing and sweating, dizziness, mild nausea and diarrhea. The heart rate was slowed but never more than 10 beats per minute and the drop in blood pressure was negligible. These reactions were stopped, without exception, within 10 to 15 minutes by the subcutaneous injection of 0.6 mg. of atropine sulfate.

We have seen several cases with extremely mild involvement or in partial or complete remission, in which the past history justified further study. In some of these even 1 mg. of neostigmine intravenously gave an indefinite response. In such cases the Curare test,<sup>6, 7, 8</sup> the Jolly test, muscle biopsy and barium swallow under fluoroscopy<sup>10</sup> have proved highly valuable. Also of some merit is a therapeutic test of a week of oral neostigmine bromide.

A preliminary report of the diagnostic use of neostigmine in myasthenia gravis was presented by the author in a case discussion published in January, 1947.<sup>11</sup>

The intravenous administration of neostigmine has consistently given more rapid, clear cut, complete improvement in cases of myasthenia gravis than we have been able to obtain with the intramuscular route as advised by Viets. A direct comparison of these methods is illustrated in figure 1. Patient 18, a 53 year old truck driver, experienced a sudden onset of severe myasthenia gravis in January, 1946, with marked diplopia and ptosis. The disease had rapidly progressed to total involvement with severe dysphagia, dysarthria and general muscular weakness when he was first seen on May 22, 1946. At the height of the disease the patient required 60 tablets of neostigmine bromide (900 mg.) daily for maximal improvement without intolerance. At the time figure 1 was taken this patient was in partial remission which has since become complete. On February 6, 1947, he was photographed after 18 hours without medication. Then 1.5 mg. of neostigmine methylsulfate and 0.6 mg. of atropine sulfate were injected intramuscularly. The patient was photographed two minutes later and then at five minute intervals for one hour. The same procedure was followed on February 7, 1947, except that 0.5 mg. of neostigmine methylsulfate was injected intravenously and no atropine was used. Two minutes after 0.5 mg. of intravenous neostigmine he showed maximal improvement whereas 60 minutes after an intramuscular dose three times as large he showed only a partial response.

Another example of the rapid effect of intravenous neostigmine is shown in figure 2. Patient 24, a 5 year old boy, experienced a sudden onset of ptosis, dysarthria, dysphagia and general muscular weakness on November 7, 1946. The referring diagnosis was tuberculous meningitis. On November 20, 1946, 0.25 mg. of neostigmine methylsulfate was injected intravenously and the patient showed complete recovery of all muscle function within three minutes. Figure 2 is taken from a 16 mm. colored motion picture film.

"A" shows the patient's condition without medication for 18 hours. "B" shows complete recovery 42 seconds after the intravenous injection of 0.5 mg. of neostigmine. This dose was well tolerated by the patient and it will be noted that his reaction was much faster than when 0.25 mg. was given.



FIG. 1. (1-6) Patient 18 in relapse, and two, five, 15, 30 and 60 minutes after 1.5 mg. of neostigmine and 0.6 mg. of atropine sulfate intramuscularly. (7-9) Patient 18 in relapse, two and 15 minutes after 0.5 mg. of neostigmine intravenously.



This rapid complete response is demonstrable not only in the facies and the extraocular muscles but also in masticatory, pharyngeal, laryngeal and skeletal musculature.

In our experience, intravenous neostigmine has given better results in the performance of the fluoroscopic barium-swallow test for dysphagia<sup>10</sup>



FIG. 2. (Left) Patient 24 in relapse. (Right) Patient 24, 42 seconds after 0.5 mg. of neostigmine intravenously.

than has intramuscular neostigmine. When barium is retained in the upper esophagus, 0.5 mg. of neostigmine is injected intravenously. If the dysphagia is due to myasthenia gravis, a return to normal swallowing can be visualized in a few minutes instead of the 20 minutes or more required with intramuscular administration.

By use of the intravenous method we have been able to illustrate dramatically the effect of neostigmine upon the myasthenic individual in a series of motion pictures taken for teaching purposes.

Medication is withheld from the patient for a period of 18 to 24 hours preceding the test. Before the injection, the routine performance tests and a "close-up" of the patient's face are filmed. Then, with the camera in continuous action, 0.5 mg. of neostigmine is administered intravenously. The performance tests are repeated at the height of the improvement which usually occurs within a few minutes. Due to the rapid and complete response to intravenous neostigmine, the progress of the patient can be recorded without the time lapse required when the intramuscular method is used.

Intravenous neostigmine has been used in the diagnosis of 24 of the cases of myasthenia gravis in our series in the past five years. Of these, 21 or 87.5 per cent, reacted sufficiently for a positive diagnosis. Only three patients failed to react. One gave a history of previous typical severe myas-

themia gravis with respiratory failure requiring a respirator. She was seen in complete remission and failed to react to intravenous neostigmine. The Jolly and Curare tests were also negative but the muscle biopsy was considered typical of myasthenia gravis. The second non-reactor had extremely mild symptoms. The Jolly and Curare tests were positive, however, and he has since responded well to oral neostigmine. The third non-reactor gave a typical history of previous severe myasthenia gravis but was seen in complete remission during his hospitalization for duodenal ulcer. His diagnosis was made on the basis of a typical history and positive Jolly and Curare tests. Objective improvement in all of the 21 reactors following 0.5 mg. of neostigmine intravenously was so rapid and clear-cut that no other diagnostic methods were necessary except to otherwise confirm a positive diagnosis.

Our experience with intravenous neostigmine in the diagnosis of myasthenia gravis leads us to believe that it has the following advantages over the intramuscular diagnostic test:

1. It gives a more rapid complete response which lessens the possibility of a false negative diagnosis in a mild case.
2. Only objective responses need be considered which diminishes the risk of false positive diagnoses.
3. The quick, clear-cut response should facilitate office diagnosis by a busy practitioner and aid in demonstration of cases for teaching purposes.

#### SUMMARY AND CONCLUSIONS

1. A new diagnostic method for myasthenia gravis using 0.5 mg. of neostigmine intravenously instead of 1.5 mg. intramuscularly, as advised by Schwab and Viets, is presented.
2. Neostigmine has been injected intravenously in several hundred cases, both myasthenic and non-myasthenic, without any serious reactions in the dosage range used.
3. Intravenous neostigmine has given objective diagnostically positive reactions in 21 out of 24 cases of myasthenia gravis in our series, or 87.5 per cent.
4. We have obtained better results with intravenous than with intramuscular neostigmine in the performance of the barium-swallow test for dysphagia due to myasthenia gravis.
5. Our experience indicates that intravenous neostigmine is superior to intramuscular neostigmine in the diagnosis of myasthenia gravis, as it gives more rapid, clear-cut and complete improvement in even the mildest cases and enables the observer to use objective criteria alone.

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# CASE REPORTS

## PRIMARY SARCOMA OF THE HEART WITH REPORT OF A CASE \*

By PALMER A. SHELBURNE, M.D., *Greensboro, North Carolina*

EIGHTY-TWO cases of primary sarcoma of the heart have been found to be reported prior to December, 1946, including 76 cases collected in excellent reviews of the literature by Perlstein,<sup>1</sup> Yater,<sup>2</sup> and Weir.<sup>3</sup> Antemortem diagnosis has been made in only five cases.<sup>5</sup> It is the purpose of this report to relate the clinical course and to describe bizarre manifestations in a patient who died of this disease after six months' observation.

### CASE REPORT

W. H. V., a white man, American, aged 29, married, was admitted to the Wesley Long Hospital, Greensboro, North Carolina, June 23, 1946, complaining of left anterior chest pain. The present illness was of 10 days' duration with sore throat,

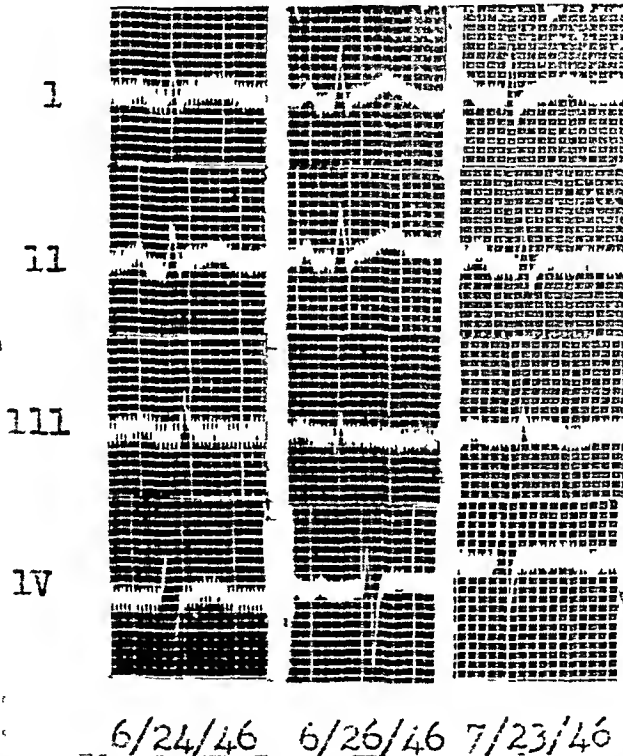


FIG. 1. Electrocardiographic tracings. June 24, 1946. Rate 120, voltage low in limb leads. PR interval .16 second. June 26, 1946. Low voltage is suggestive of pericarditis but may occur in normal hearts, myxedema and severe myocarditis. July 23, 1946. Rate 80. Digitalis effect. PR interval .18 second. T-wave inverted in Lead III and flat in Lead II.

\* Received for publication June 13, 1947.

cough and low fever, but he had been able to work until three days prior to admission. He had had fever and chills at the age of 15 years, diagnosed as tertian malaria; an abscessed tooth with drainage for one year; and during the same period of time suffered three attacks of momentary unconsciousness, preceded by weakness and irregular pulse, with apparent improvement following ingestion of food rich in carbohydrate.

*Physical Examination.* Cyanosis and dyspnea were evident. Temperature was 100.5° F. Blood pressure was 90 mm. Hg systolic and 75 mm. diastolic. The area of cardiac dullness was enlarged. The left border was in the sixth intercostal space, 4 cm. to the left of the midclavicular line, the right border 4 cm. to the right of the

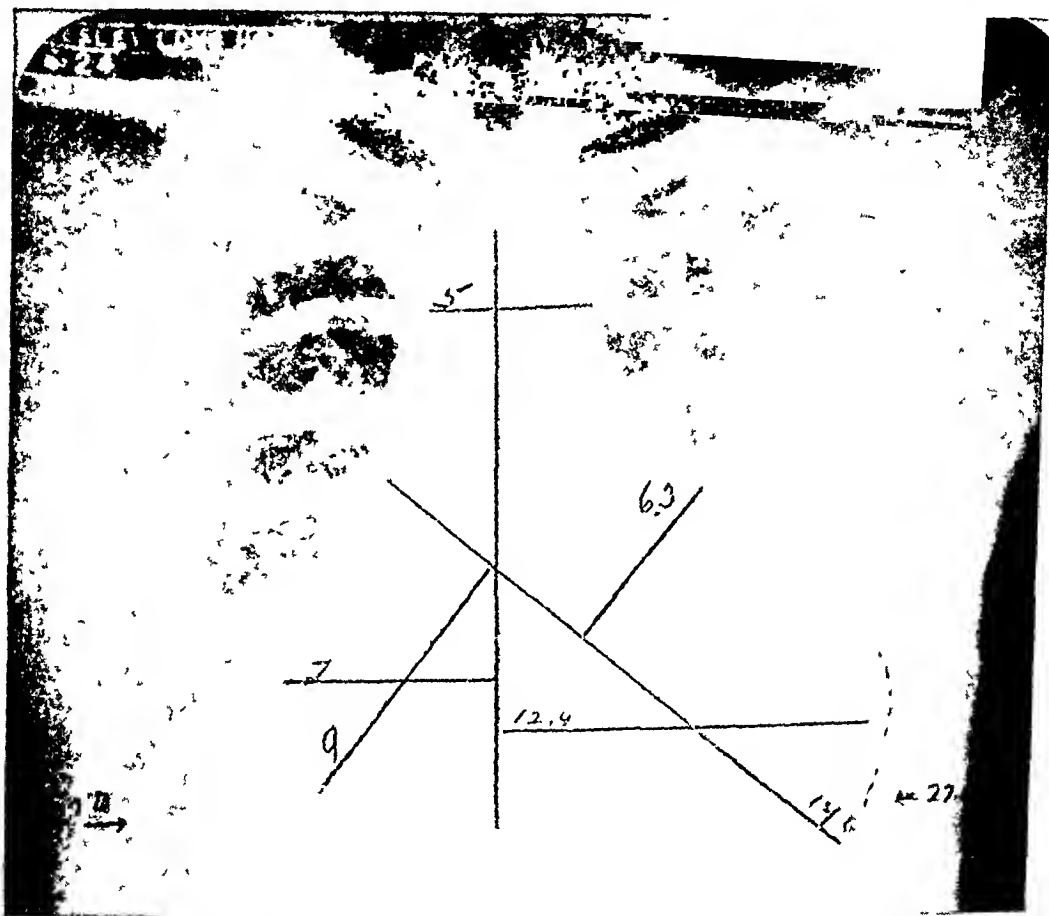


FIG. 2. Roentgenogram. Cardiac silhouette is enlarged. Note absence of mitral configuration and the more or less symmetrical "leather-bottle" outline of heart shadow.

midsternal line. The apex beat was diffuse, the heart sounds distant, and a friction rub could be heard and felt over the base of the heart. Bronchial breathing and dullness could be heard just below and medial to the tip of the left scapula (Ewart's or Bamberger's sign). The left knee was tender and showed some limitation of motion. There was no redness nor swelling. Red blood cell count was 4,790,000; hemoglobin 15 grams; white blood cell count 15,200; polymorphonuclear cells 76; eosinophiles 1; small lymphocytes 23 per cent. Sedimentation rate was 22 mm. in one hour (Cutler); Kahn reaction was negative; blood culture was sterile after five days.

*Clinical Course.* A pericardial paracentesis was performed on the second and fourth hospital days because of great dyspnea. A total of 2100 c.c. serosanguineous fluid was obtained. In each instance withdrawal of fluid relieved dyspnea, slowed

the pulse rate to 100, and raised the blood pressure to 120 mm. Hg systolic and 80 mm. diastolic. The fluid clotted after standing 24 hours. A guinea-pig was injected in an effort to learn if the condition were tuberculous. From time to time there could be heard varying types of heart sounds over the chest; systolic and diastolic mitral murmurs and pericardial friction rubs, each of which showed great variation and even disappearance with time and change of position. A tentative diagnosis of rheumatic fever or generalized septicemia was made.

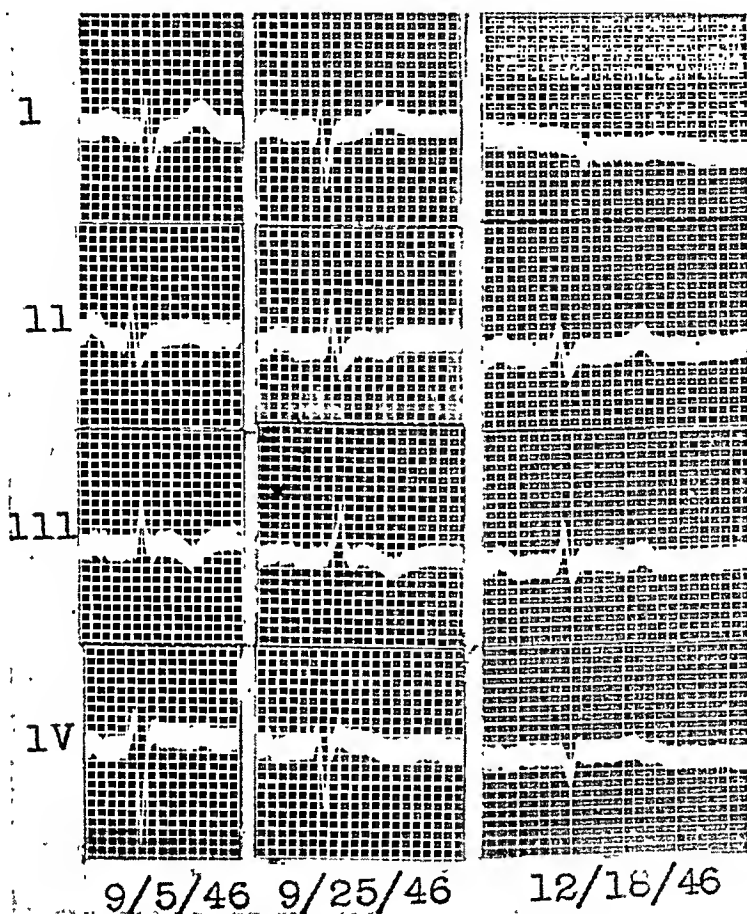


FIG. 3. Electrocardiographic tracings. September 5, 1946. A shift from normal axis to right axis deviation had become evident. PR interval 0.2 second. September 25, 1946. Rate 60. T-wave in Lead II and Lead III inverted. Notching of P-wave in Lead II. December 18, 1946. Rate 50. PR interval 0.24. Beginning auricular ventricular block. T-waves in Lead II and Lead III now upright. Inversion and return to normal are suggestive of myocardial infarction. The electrocardiographic tracings were not typical of any disease entity.

Medication consisted of sodium salicylate and sodium bicarbonate, of each 1.3 gm. (20 grains), every four hours. Pantopon 0.002 gm. ( $\frac{1}{8}$  grain) was required for chest and joint pain. The joints involved were, alternately, the knees, the right shoulder, and the right elbow. There was no swelling or redness of the involved joints. Roentgenogram of the right shoulder was negative. Salt restriction, with limitation of fluid, prevented further pericardial effusion.

On the seventh day of illness the patient was sitting erect in bed when a dramatic episode occurred. Pulse deficit for the first time had been noted. A few minutes following this observation the patient suddenly became pale, then cyanotic, then lost

consciousness. The radial pulse was slow and irregular. The heart sounds were distant, irregular and of slow rate. Death seemed imminent. A convulsive seizure lasting 10 minutes followed, and the patient was forcibly held in bed. Death may have been averted by the following procedures: Patient was placed in the Trendelenburg position; adrenalin was given by intravenous injection, oxygen and artificial respiration. Finally the patient gave a forceful expiratory grunt; the heart rate increased until accurate counting was impossible and consciousness was regained. The paleness, slow irregular heart beat and syncope were suggestive of Adams-

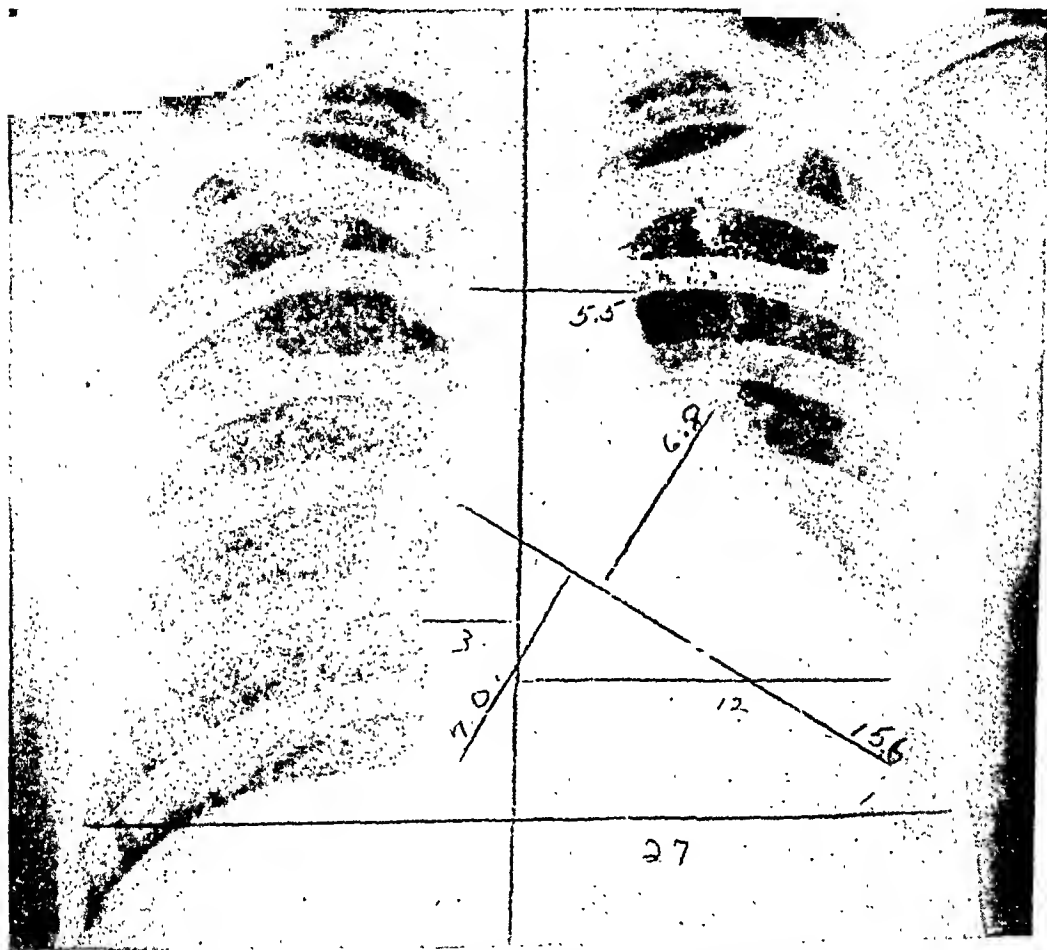


FIG. 4. Roentgenogram. There is no evidence of pericardial effusion at this time. The right border of the heart is normal, but the left border is definitely prominent and has a mitral configuration.

Stokes syndrome. The rapid heart rate was suggestive of ventricular tachycardia. A satisfactory explanation of the cardiac arrhythmia could not be made at the time of its occurrence. The patient stated that on three occasions in the past year he had experienced weakness, irregular pulse and momentary unconsciousness, and that ingestion of food rich in carbohydrates appeared to aid in recovery. Because of this history glucose was given intravenously. Repeated blood sugar determinations, however, suggested this attack was not due to hypoglycemia.

Following this attack the patient was digitalized and a daily maintenance dose of .2 mg. digitoxin was given. In spite of this the pulse remained 80-100. At intervals oxygen was administered to combat cyanosis and dyspnea. A total of 25,-





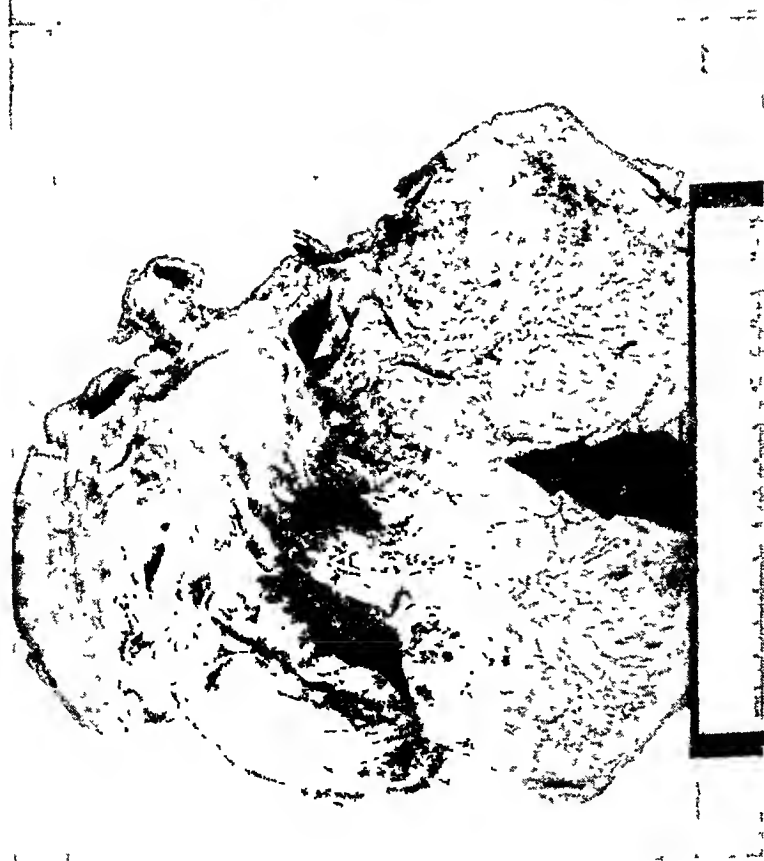


FIG. 6. Heart sectioned to show necrotic tumor making up thickened right ventricular wall, and (A) tumor mass projecting into cavity.



FIG. 7. Section showing left side of heart with extensive involvement of auricular walls and focal areas of tumor in the ventricular wall.

to 100 under digitalization, 40 to 120 when this drug was not being administered. Digitalis was discontinued after three and one-half months of administration. Three weeks later an unexpected bradycardia of 40 to 50 was noted. This slow rate continued for two weeks and reappeared when evidence of heart block was noted.

After five months of illness, graduated exercises were prescribed but were soon discontinued when the cardinal symptoms of heart failure developed. An interesting feature was the almost entire limitation of edema to the face and upper extremities. The patient became unconscious December 17, 1946 and died in cardiac failure after 180 days of illness.

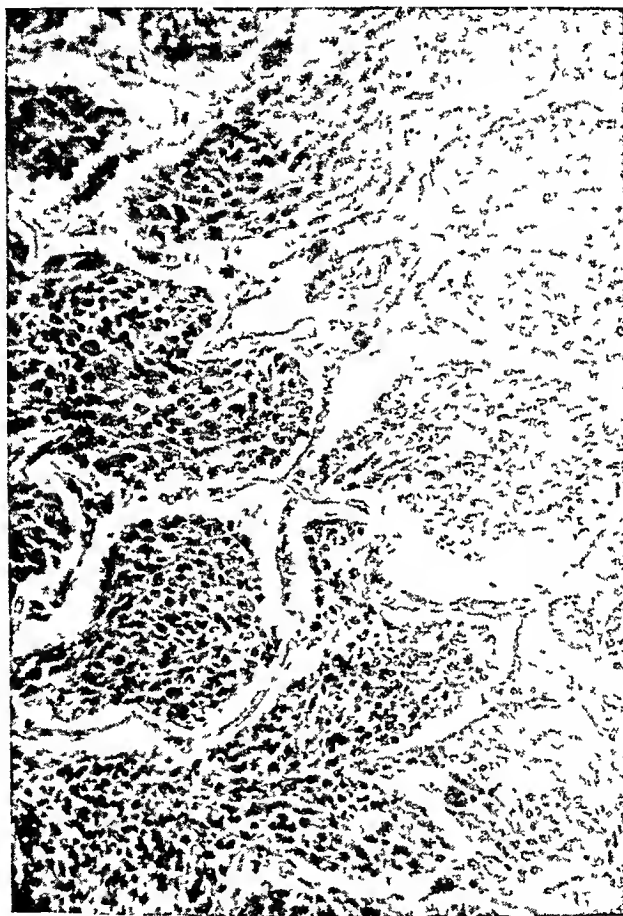


FIG. 8. Low power view of metastatic lesion in right lung.

*Autopsy Report.* The significant findings at autopsy were a moderate generalized anasarca, bilateral hydrothorax, and some ascitic fluid in the abdominal cavity.

**Lungs:** Both lungs showed some atelectasis as well as considerable congestion. In the peripheral portion of the right lung were four small well-demarcated tumor nodules varying from 5 mm. to 10 mm. in diameter.

**Heart:** The pericardial cavity was completely obliterated by old fibrous adhesions. The heart with its pericardial covering weighed 1500 grams, its shape was greatly distorted, its surface nodular. Upon opening the heart the right auricular cavity was found to be greatly enlarged, and the wall thickened by an infiltrating tumor. The right ventricular wall was practically replaced by a neoplastic growth which showed extensive necrosis. Practically the entire myocardium had been replaced by tumor.

tissue and the wall measured up to 10 cm. in thickness. There was a large tumor mass, rather necrotic, growing from the wall into the right ventricle, practically filling this chamber, and pointing upward, partially occluding the orifice of the pulmonary artery. The left side of the heart showed extensive involvement of the auricular wall, this averaging 3.5 cm. in thickness. There were also isolated areas of tumor tissue in the myocardium of the left ventricle. The valves all appeared competent and showed no evidence of disease. The liver and spleen showed congestion.



FIG. 9. Low power view of primary tumor in the myocardium.

Microscopic study of the heart sections and the tumor masses found in the lungs revealed that they were neoplastic growths made up of ovoid and spindle-shaped cells. Extensive necrosis affected a greater part of the tumor tissue. The myocardium showed definite invasion by the neoplastic process. No demonstrable striations of the tumor cells were found.

Pathological Diagnosis: Primary fibrosarcoma of the heart, with pulmonary metastases.

#### COMMENT

Tumor tissue with its attendant edema involving the entire wall of the right auricle may have interfered with impulses reaching the sino-auricular node producing bradycardia. A similar interference with the conduction system distal to the sino-auricular node may have caused beginning auriculoventricular block.

The growth of tumor tissue into the cavity of the right ventricle was of sufficient size to close the pulmonic valves momentarily. It is possible that the attack of unconsciousness was produced by stoppage in the flow of blood through the heart in this manner and that relief followed a change in position.

*Differential Diagnosis.* Negative blood and pericardial fluid cultures, a normal guinea-pig two months after injection with pericardial fluid, negative lung fields and negative tuberculin test eliminate septicemia, tuberculous pericarditis and subacute bacterial endocarditis. Lack of evidence of enlargement of the spleen or of the mediastinal glands, and the moderate increase in number of white

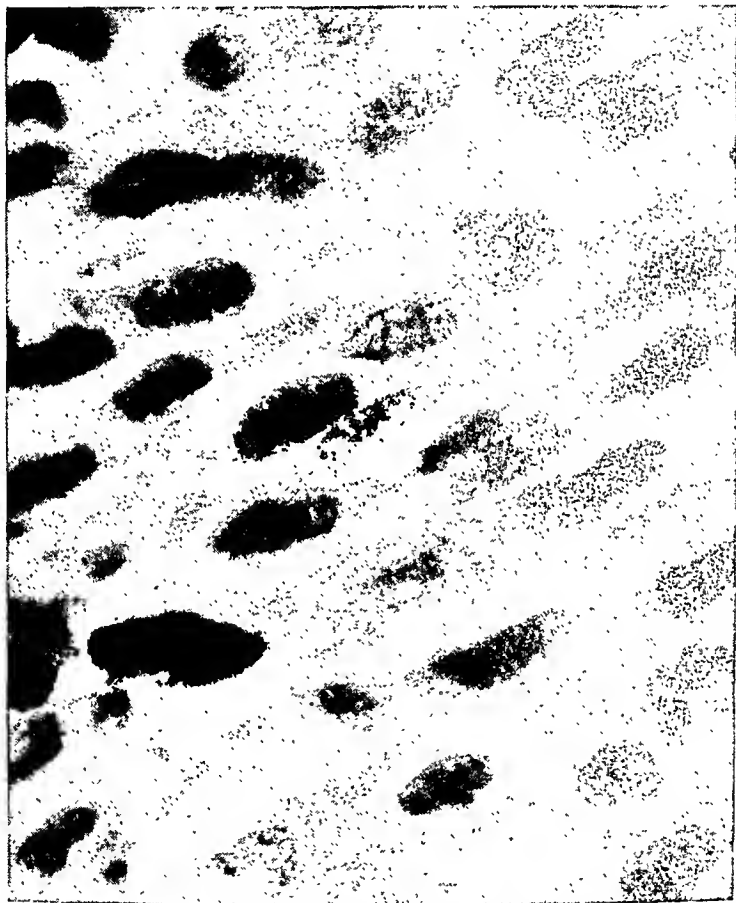


FIG. 10. High power view of myocardial tumor showing a typical area of sarcomatous process.

blood cells with a normal differential count, were considered sufficient to eliminate leukemia and Hodgkin's disease as a cause of the pericardial effusion early in the illness. Rheumatic fever was considered the most likely diagnosis because of the following findings: *Major manifestations* (1) carditis, evidenced by pericardial effusion, enlargement of the heart, and decompensation; prolongation of auriculoventricular conduction time, T-wave inversion, low voltage, sinus tachycardia and bradycardia; and (2) arthralgia preceded by sore throat. *Minor manifestations* (1) fever, (2) precordial pain, (3) increased white blood cell

count, and (4) increased sedimentation rate. It was recognized that rheumatic fever did not explain the complete picture. Recurring attacks of syncope and unconsciousness, and bradycardia were manifestations requiring autopsy for adequate explanation.

The sudden onset of signs of intractable heart disease in a young person without a history of preëxisting cardiac disease, with no discoverable basis for the disease; a rapidly forming serosanguineous pericardial fluid; postural alteration in murmurs and pericardial friction rubs; roentgenologic evidence of increasing heart enlargement and irregularity of shape; failure of pulse rate to respond to adequate digitalization; attacks of syncope; cardiac arrhythmias, including sinus tachycardia, bradycardia and beginning heart block should lead one to consider neoplasm of the heart as a possible cause of the disease under consideration. The finding of cancer cells in the pericardial fluid enables one to make a positive diagnosis, but, unfortunately, this study was not made in this case.

### SUMMARY

A case of primary fibrosarcoma of the heart is reported. Attention is called to bizarre clinical manifestations which, possibly, might have led to antemortem diagnosis.

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## A CASE REPORT OF METASTATIC CARCINOMA TREATED WITH TEROPTERIN\*

By MAX J. KLAINER, M.D., F.A.C.P., *Stoneham, Massachusetts*

IN the years prior to the use of sulfonamides and more especially to the use of penicillin, infrequent reports of "cures" of individual cases of subacute bacterial endocarditis appeared in medical literature. As with subacute bacterial endocarditis in former years, metastatic carcinoma invariably has been fatal so that any therapy which gives a modicum of evidence of checking the spread of this fatal disease deserves consideration. It is, therefore, of interest to report a case of metastatic adenocarcinoma which apparently had been temporarily arrested and by the use of a new chemotherapeutic approach.

### CASE REPORT

A 39 year old Armenian housewife first was seen in February 1947 because of severe, agonizing pains originating in the region of the lower lumbar spine and



FIG. 1.

\* Received for publication December 26, 1947.  
Teropterin is the name given by Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York for pteroyl triglutamic acid.



FIG. 2.

radiating down the posterior aspect of the left thigh and left leg to the heel. A left radical mastectomy had been performed by Dr. Richard Miller at the Massachusetts General Hospital, Boston, in December 1944 because of an adenocarcinoma Grade III with spread to the axillary lymph nodes. The patient had made a good recovery from the operation and had done well until March 1946 when pain developed in the region of the mid-lumbar spine, and roentgen-ray studies revealed a destructive process in the third lumbar vertebra. The patient then was given radiotherapy over a period of several months without any appreciable improvement. Roentgenographic

studies repeated in September 1946 showed extension of the process in the third lumbar vertebra and new areas of destruction in the dorsal vertebrae and the ribs. A diagnosis of metastatic carcinoma was made and the patient placed on narcotic medication for relief of pain. However, she became progressively worse and soon was bedridden. She was unable to make the slightest movement without severe pain.

The patient's condition seemed hopeless and she was hospitalized primarily for the purpose of being kept as comfortable as possible. On admission to the Sanitarium and Hospital, Stoneham, Massachusetts, the patient proved to be a trying nursing problem. Only by lying quietly on her right side with her knees drawn to her abdomen could she endure her pain. Changing the bed linen, bathing, and the use of the bedpan were almost impossible. In addition she sweated profusely, necessitating frequent changes of the sheets. One hundred mg. demerol and dilaudid in doses of grains 1/16 every four hours only partially controlled her pain.



FIG. 3.

Physical examination at the time of admission revealed percussion tenderness along the lower dorsal and lumbar vertebrae and along the course of the left sciatic nerve. The eyes, ears, nose and throat, heart, lungs and upper extremities were all within normal limits. The blood pressure was 140 mm. of mercury systolic and 90 diastolic. The temperature 98.6°, pulse 100 and respirations 20 per minute.

Initial laboratory studies disclosed the following: hemoglobin, 12 gm. (77 per cent Sahli); red blood count, 3,660,000; white blood count, 5,450 with 40 per cent polymorphonuclears and 58 per cent lymphocytes. The total serum protein was 6.3 grams with 3.0 grams albumin and 3.3 grams globulin. No Bence Jones protein was found



in the urine, and the urinalyses were not otherwise remarkable. In spite of extensive bone destruction the acid phosphatase was essentially normal, 4.5 King units.

Roentgen-ray films of the dorsal and lumbar spine, ribs and pelvis showed innumerable areas of bone destruction with pathological fractures of several of the ribs and of the eighth dorsal and second and third lumbar vertebrae (figures 1, 2 and 3). Areas of bone destruction also were found in the skull and in the right scapula. In an effort to check further bone destruction, the patient was placed on 50 mg. testosterone propionate and 20 mg. Teropterin three times a day, each being administered intramuscularly.



FIG. 4.

During the first week of her hospital stay the patient had her usual menstrual period and with the onset of the menses the pain increased markedly. An oophorectomy appeared advisable, and this was performed successfully on March 3, 1947 by Dr. Raymond Auvil of the hospital staff. At the time of operation the uterus was found to be enlarged, but there were no masses in the liver or elsewhere in the abdomen. Pathological studies of the removed tissues revealed normal Fallopian tubes but sections of the ovaries showed foci of metastatic adenocarcinoma.

In the first two weeks following operation the patient showed little change and she continued to require large doses of narcotics for relief of pain. During this time, however, the testosterone propionate was reduced to 100 mg. daily but the Teropterin was continued at 60 mg. daily. On March 17, 1947 she was given a transfusion of 500 c.c. of citrated blood with prompt return of the hemoglobin and red count to normal levels.

The first evidence of improvement was noted on March 19, 1947. The pain became less marked, the sweats were markedly reduced, and the patient became more cheerful. About March 23 she suffered a slight setback with accentuation of pain, but this was attributed to her expected menstrual period. Immediately thereafter



FIG. 5.

progressive and marked improvement was noted. By April 1, 1947 practically all narcotic medication for relief of pain was eliminated and the testosterone medication completely discontinued. The patient now received only Teropterin intramuscularly, while barbiturates were given for sedation and aspirin compound tablets for control of pain. During the period of testosterone therapy this patient did develop secondary sex changes such as hirsutism and deepening of the voice. These, however, slowly disappeared upon discontinuance of this drug. On April 11 this patient, who

had been unable to move without extreme pain, changed position freely in bed. On April 14 she sat up in a wheel chair.

Repeat roentgen-ray studies of the involved bones done on April 20 were interpreted as follows: "Reëxamination of the skeletal system shows no significant increase in the areas of bone destruction. As a matter of fact several of the previously described areas of bone destruction appear smaller and there is new bone formation seen in several areas where the destruction was markedly pronounced. Several of the pathological fractures show evidence of bony regeneration. The compression fractures of the second and third lumbar vertebrae are still present as previously described but the bone structure is somewhat denser" (figures 4 and 5).

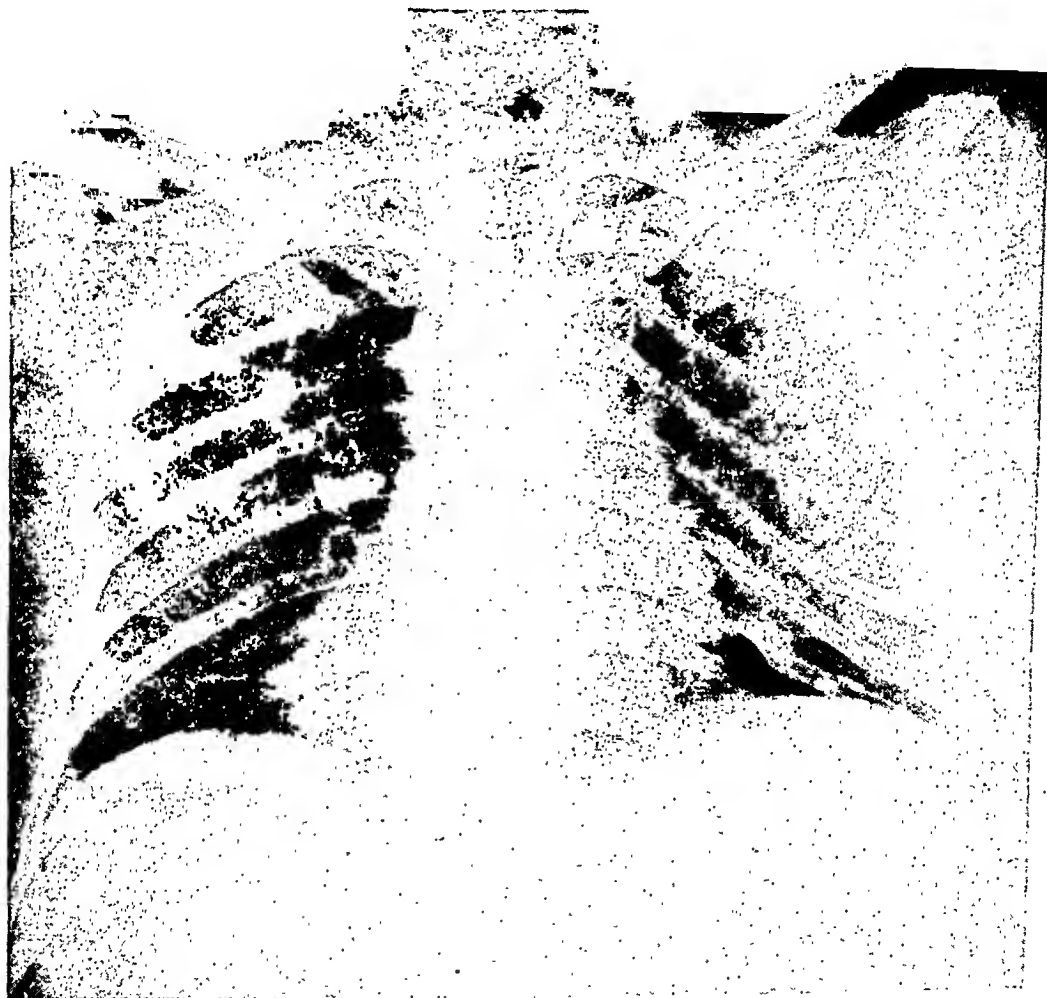


FIG. 6.

In May 1947 the patient was measured for a back brace. On May 14 she was allowed to walk first with the aid of a walker, and then with a cane only. This increase in activity produced no increase in the small amount of residual discomfort, and on June 5, 1947 she was discharged home on a maintenance dose of Teropterin 20 mg. b.i.d.

Roentgen-rays taken at the time of discharge were interpreted as follows: "Films of various bones show a remarkable change in the appearance of the bone structure with disappearance of many of the previously described areas of bone destruction,

with recalcification of the bone and healing of many of the fractures, particularly of the ribs. The bone structure of the involved lumbar vertebrae has improved due to increased recalcification. The findings as a whole indicate a very marked improvement in the previously described findings of pathological fractures and metastases."



FIG. 7.

Following discharge from the hospital the patient continued to improve both clinically and by roentgen examination. Except for her back brace she was able to walk without the aid of any support and could perform many of her previous household duties. Except for transitory aching in the region of the left hip, which was readily relieved by an aspirin compound tablet, she was free of symptoms. The Teropterin medication was continued with a daily maintenance injection and she learned to

administer it to herself. Roentgen-ray films that were taken in October 1947 showed no new areas of bone destruction and further regeneration of bone formation in areas previously involved (figures 6, 7, and 8). In December 1947, the patient continued to show improvement, being completely ambulatory and complaining only of mild aching in the lumbar spine on prolonged standing or walking.



FIG. 8.

In January 1948, however, the patient returned to the hospital because of a recurrence of pain in several ribs on the left side and roentgenograms revealed new areas of metastasis involving multiple ribs. The Teropterin therapy was intensified for several weeks with some alleviation of the pain, but by March 1948 evidences of bone metastases were again present in the pelvis, vertebral column and left femur. The Teropterin no longer was able to control the pain and narcotic medication had to be resumed. The patient became increasingly depressed and voiced suicidal intentions. In May 1948 she threw herself forcibly from bed sustaining several pathological fractures and she died in shock within 24 hours.

An autopsy was performed and revealed gross involvement of the right breast, the lungs and the adrenal glands as well as of multiple bones. Microscopic study revealed that the carcinoma was scirrhus in character; that in the lungs the metastases showed areas of focal necrosis; in the bones along with extensive replacement and destruction there was evidence of new bone formation; and in all areas only occasional mitotic figures were seen.

## SUMMARY

A case is reported of a 39 year old woman with metastatic spread of an adenocarcinoma, presumably originating in the breast, in whom the combined use of oophorectomy, testosterone propionate injections (given only during the first month of therapy), and injections of a new compound known as Teropterin (pteroyl triglutamic acid) produced definite clinical and roentgenological improvement which persisted for 10 months. The subsequent course of the patient was downward, and she died 14 months after therapy was instituted. Necropsy studies revealed gross involvement of the right breast, of the lungs, the adrenal glands and of multiple bones but microscopic studies revealed only occasional mitotic figures in the involved areas, evidences of focal necrosis in the metastatic areas in the lungs and evidences of new bone formation in the involved bones.

The author wishes to thank the medical and nursing staff of the New England Sanitarium and Hospital whose help in the management of this case was of great value.

Teropterin was supplied for clinical study by Dr. Y. SubbaRow, Director of Research, and his staff at Lederle Laboratories Division, American Cyanamid Company, to Dr. S. Farber of the Children's Hospital, Boston. I wish to express my thanks to Dr. J. Hawkins, formerly associated with Dr. Farber, for my original supply of this material.

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THE DIAGNOSIS OF METASTATIC TUMOR BY CYTOLOGICAL EXAMINATION OF THE PERICARDIAL FLUID;  
REPORT OF A CASE USING SHORR'S STAIN \*

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METASTATIC tumors of the heart and pericardium are not uncommon. Reports of their incidence vary from 6.2 per cent to 10.9 per cent of all malignant disease.<sup>1, 2</sup> There are, however, few reports of the antemortem diagnosis of this condition, since such a diagnosis depends not only upon the suspicions of the clinician, but also upon the demonstration of neoplastic cells in the heart or pericardium. Perhaps the most important diagnostic aid is the cytological study of pericardial fluid. Pericardial effusion is often, though not regularly, present. Even by this method the number of instances in which an accurate antemortem diagnosis has been made is small, there being only 10 cases reported in the American literature.<sup>3, 4, 5</sup>

For some years we have been interested in the study of exfoliated cells in body secretions and fluids with particular reference to the demonstration of malignant neoplastic cells in such materials. The method employed is simple and has given us accurate results in a high percentage of cases, especially in the study of sputum.<sup>6</sup> The following case of bronchogenic carcinoma in which tumor cells were found in both sputum and pericardial fluid by means of stained wet films seems worth reporting.

\* Received for publication April 6, 1948.

From the Departments of Anatomy and Medicine, Albany Medical College, Union University, and the Medical Service, Albany Hospital.

The method is Shorr's technic for the wet film study of vaginal smears.<sup>7</sup> Fresh material is spread on a glass slide and fixed before drying for a minimum of 10 minutes in a fixative made of equal parts of 95 per cent alcohol and ether. Smears of sputum must be made fairly thin if the mucus is tenacious and thick, as fixation as well as staining is difficult in these cases. Aspirated fluids are centrifuged and the sediment used; when smearing the sediments an attempt should be made to remove the buffy coat with a minimum of red blood cells as an excess of the latter element may completely obscure the other material. A second set of smears from fluid sediments is routinely fixed in a fixative made of 95 c.c. of the above alcohol-ether fixative to which has been added 10 c.c. of glacial acetic acid. This hemolyzes the red blood cells but fixes neoplastic and other nucleated cells without distortion. There is, however, a tendency for the cells in certain cases to stain less vividly after the acid treatment. An alternate method of hemolyzing the red blood cells in aspirated fluids is the addition of the acetic acid before centrifugation; 50 per cent acetic acid is added to the fluid using about 1/20 the volume of the fluid to be examined or enough acetic acid to give complete hemolysis in about five minutes. In the case presented below, although all three methods were used the latter proved most successful.

After fixation the slides are stained for two minutes in Shorr's single differential stain, dehydrated by dipping 10 times in 80 per cent and 95 per cent alcohol, cleared in xylol, and mounted in damar with a cover slip as described by Shorr. Although the technic was originally developed for use with vaginal smears, because of the sharp differentiation given between cornified and non-cornified cells, we have found that this particular formula of Shorr's stain is an excellent nuclear stain and much more delicate than the hematoxylin-eosin stains. As the stain is a mixture of four acid dyes (Biebrich scarlet, orange G, fast green, and aniline blue) it affords no information as to the degree of acidophilia or basophilia. The cytoplasm stains green to green-blue in non-keratinized cells and specifically pink with the Biebrich scarlet in keratinized cells. Younger cells and those having apparently increased metabolic activity stain more deeply. The chromatin of the nuclei stains red-brown and may be quite dark while the nucleoli when present usually take on a translucent deep red or more rarely an olive green color.

Among the cells in fluids aspirated from serous cavities the mesothelial cells should first be mentioned because of their prominent nucleoli and their wide range of appearance in the presence of irritative phenomena. They may usually be differentiated from neoplastic cells because their chromatin clumps and nucleoli are smaller than those of tumor cells. In the case of sputum the morphology of the accumulated exfoliated cells in the respiratory and pharyngeal secretions is at first confusing, but there is a relative homogeneity within the various non-malignant cell groups. Against the background of pale blue stained mucus are seen the major cellular constituents of sputum: leukocytes, exfoliated squamous epithelial cells and large phagocytes. The leukocytes and epithelial cells look much the same as in vaginal smears and need no description. The phagocytes, whose oval shape and yellow-green cytoplasm are distinguishing features, contain ingested material or small vacuoles and vary considerably in size though little in chromicity; they are often bi- or tri-nucleate with one or two nucleoli. Other non-malignant cells which may be identified are ciliated columnar epithelial cells and metaplastic squamous cells.

Malignant neoplastic cells appear as atypical cells showing distortions of shape, variation in chromicity and certain other characteristics by which they may usually be identified. The cytoplasm often shows faint concentric rings, vacuoles, perinuclear paling, or in large cells a dark green perinuclear ring. There are marked variations in the nuclear-cytoplasmic ratio; the nuclei are often large with large irregular nucleoli. There is a tendency toward clumping of the chromatin and toward what appears to be the fusion of several nucleoli. The chromatin associated with the nucleolus usually is more dense than in non-malignant cells. The cells may appear singly or in small syncytial groups. Occasional extremely bizarre forms are encountered which reflect the exuberant growth of the neoplasm and present no trouble as to their identity.

The diagnosis of cancer depends, however, not upon finding a single pathognomonic cell but on finding many of them or on finding several small clusters of them. Caution must be observed in making a diagnosis of cancer in the presence of chronic inflammation and metaplasia since confusion may arise between "borderline" cancer cells and non-neoplastic atypical cells. This same difficulty, of course, is encountered in tissue sections.

#### CASE REPORT

A 61 year old white man was admitted to the Albany Hospital on August 24, 1946. Four months previously he had coughed up thick, bright red sputum which was followed by intermittent dull right chest pain radiating to the scapula, increasingly productive morning cough, anorexia, weakness, epigastric fullness, and a 30 pound weight loss. The urge to cough was increased when lying down and, just before admission, was productive of about two ounces of sputum daily.

Past medical history revealed a gonorrheal infection as a youth and hoarseness for 35 years following "influenza."

On physical examination the blood pressure was 108 mm. Hg systolic and 70 mm. diastolic, pulse 80, respirations 24, temperature 100.4° F. The patient was a well developed white male in no acute distress, but showing signs of recent weight loss. His voice was very hoarse. There were a few telangiectases on the cheeks and thorax. No lymphadenopathy was noted. The trachea was in the midline. The chest was emphysematous but symmetrical. The lungs were resonant to percussion but inspiratory wheezes and rhonchi, as well as râles and bronchovesicular breath sounds, were heard over the right upper chest anteriorly and posteriorly. The wheeze was heard best anteriorly. The heart was not enlarged, showed normal sinus rhythm and no murmurs or friction rub. Examination of the abdomen revealed only that the liver was palpable on deep inspiration. Rectal examination was not remarkable.

Neurological examination was entirely within normal limits.

Examination of the blood showed 13 gm. hemoglobin, 4,200,000 red blood cells and 7000 white blood cells with a differential count of 86 per cent polymorphonuclear cells, 9 per cent lymphocytes, 4 per cent monocytes, and 1 per cent eosinophiles. Non-protein nitrogen was 34 mg. per cent. Blood Wassermann test was negative. Urinalysis was not remarkable. Eight sputum examinations were performed, one of which was reported as showing a single tubercle bacillus. *Streptococcus viridans* was cultured from the sputum. Chest roentgenograms on admission showed a large cavity occupying the upper lobe of the right lung. The pleura along the axillary portion of the chest and in the interlobar fissure was thickened. There was a fluid level in the cavity.



The patient was given postural drainage and aerosol penicillin inhalations, 30,000 units every three hours throughout his hospitalization with resultant reduction of the sputum from 55 gm. to 25 gm. daily.

On August 30, bronchoscopy was performed and all the bronchi appeared normal. Secretions aspirated at bronchoscopy were sent to the pathological laboratory where no tumor cells were found in preparations stained with hematoxylin and eosin.

Electrocardiogram taken on September 16 showed left axis deviation associated with evidence of heart muscle damage probably on the basis of arteriosclerosis (low slurred  $R_1$ , slightly elevated  $ST_1$ , low  $T_1$ , slurred  $QRS_{2 \text{ and } 3}$ , low  $R_4$  and depressed  $ST_4$ ).

The patient felt unimproved and one month after admission began to complain of intermittent pain in both arms as well as the chest. On October 1, hyperactive right knee and ankle jerks, with slight weakness of the right arm and leg, were found. The heart sounds were very distant; no murmurs or friction rub were heard. Blood pres-



FIG. 1. Anterior-posterior roentgenogram of the chest taken October 2 showing enlargement of the heart shadow, obliteration of the left costophrenic angle, and the thickened interlobar fissure on the right. The cavity in the right upper lobe is poorly defined.

sure was 120/70, pulse 80, respirations 20. One plus pitting pretibial edema was noted. Chest roentgenograms at this time (October 2) showed fluid in the left pleural cavity and enlargement of the heart shadow (figure 1). Fluoroscopy revealed diminished pulsations particularly in the left ventricular segment of the cardiac contour. Electrocardiogram taken at the same time was described as showing increase in heart muscle damage due either to an anterior wall infarction or a pericardial effusion. ( $R_1$  was seen to be lower and thicker,  $T_1$  diphasic and lower,  $ST_1$  more elevated,  $Q_3$  more shallow (3 mm. in depth) and slurred, and  $T_4$  diphasic.) Lumbar puncture performed because of the reflex changes gave normal chemical and cytological findings.

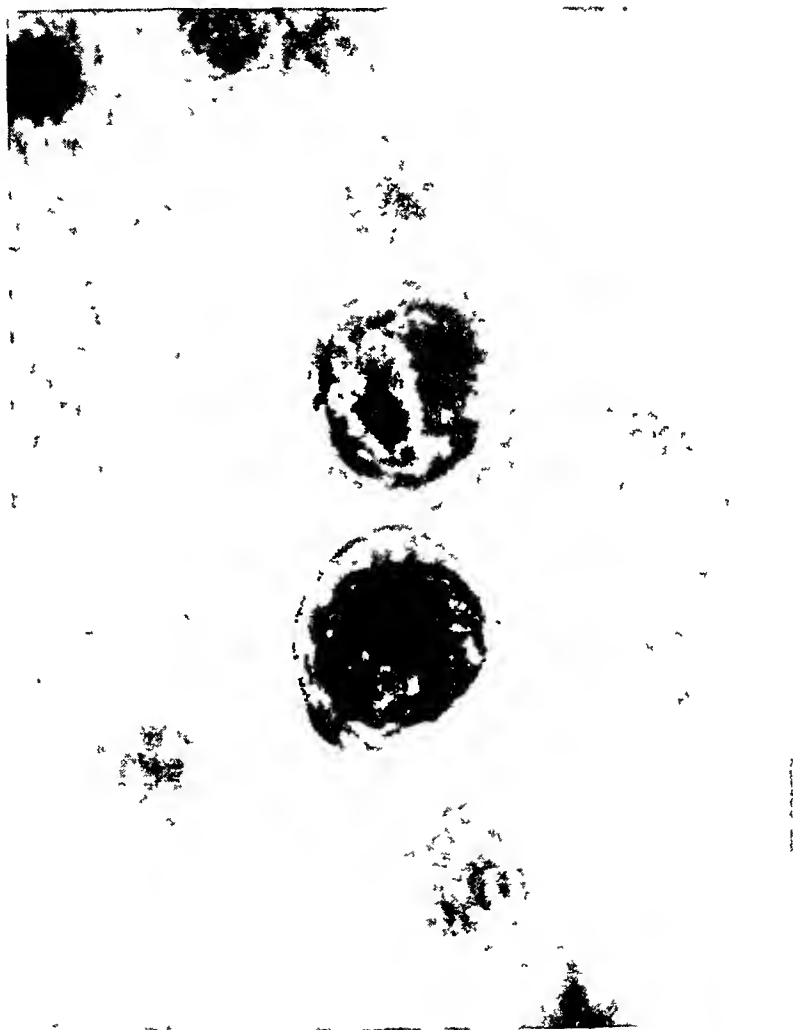


FIG. 2. Two cancer cells, sputum smear (Shorr's stain). Note the concentric irregular refractile rings in the cytoplasm, the increase in the nuclear cytoplasmic ratio, the coarse chromatin clumping, the large irregularly shaped nucleoli.  $\times 1650$ .

On October 1, a sputum was submitted to one of us (F. D. McC.) for smear and examination. This revealed many atypical cells, singly and in small groups, that showed marked variation in size and density of both cytoplasm and nucleus; a few of these atypical cells were keratinized. There were many cells with large, irregular nuclei with one or more large nucleoli. The chromatin of these nuclei showed

moderate clumping and stained brown to black in contrast to the red-brown nuclei of the normal cells (figures 2 and 3). On the basis of these findings a diagnosis of bronchogenic epidermoid carcinoma was made.

On October 7, because the patient complained of increasing dyspnea and epigastric fullness and because a paradoxical pulse, a blood pressure of 100/78, and distant heart sounds were now found, a pericardial tap was performed. The pericardium was entered at the fifth left interspace in the anterior axillary line and yielded 250 c.c. of bloody non-clotting fluid with slight relief of the patient's discomfort. Further peri-



FIG. 3. A cancer cell, sputum smear (Shorr's stain). Note the irregularly folded nucleus with the surrounding ring of dark staining cytoplasm and the dense clumping of the chromatin about the nucleolus.  $\times 1650$ .

cardial taps were performed on October 17 and 23, yielding 200 c.c. and 300 c.c. of bloody fluid respectively. The tap done on October 23 was performed by entering the pericardium from below by inserting the needle just to the left of the xiphoid because all attempts to enter the pericardial space by the previous route now failed. No tubercle bacilli were found in the pericardial fluid.

At the time of each pericardial tap about 15 c.c. of fluid were submitted for examination by our method, the rest being sent to the pathological laboratory where

it was spun down for cell block study (hematoxylin and eosin stain). Of the cell block studies those of the first two specimens were said to show no tumor cells while those of the third showed cells which were considered to be malignant but of unknown origin. However, in all three specimens of pericardial fluid smeared and stained with Shorr's stain atypical cells were found, many of which were identical with the non-keratinized cells seen in the sputum and confirmed the now suspected diagnosis of bronchogenic epidermoid carcinoma metastatic to the pericardium (figures 4 and 5).



FIG. 4. A cancer cell from a smear of the pericardial fluid withdrawn on October 7 (Shorr's stain).  $\times 1650$ .

The patient's subsequent course was rapidly downward. He developed venous distention and edema of the upper extremities, severe pain in the right arm, marked dyspnea, and cyanosis. Death occurred on October 28, 1946.

At necropsy the upper lobe of the right lung was found to be adherent to the chest wall. There were 1500 c.c. of dark brown fluid in the left pleural cavity and 1000 c.c. in the right. The contents of the mediastinum were normally disposed but were obscured by the presence of much firm fibrous tissue, firm gray tumor nodules, and enlarged lymph nodes. The pericardial cavity was almost completely obliterated by

invasion with tumor tissue. Both cardiac ventricles were hypertrophied, particularly the right, and the tumor was seen to have invaded the myocardium of the right ventricle. The right auricle was contracted due to invasion of the superior vena cava which was itself completely occluded by the new growth. While the aorta was surrounded by tumor tissue the intima was not invaded. The right lung showed extensive scattering of tumor nodules over the pleural surface; the two lower lobes were firm and non-crepitant and the upper lobe was found to consist almost entirely of a large cavity surrounded by tumor tissue which appeared to originate in the right upper lobe bronchus at its junction with the right main bronchus. The left lung also showed



FIG. 5. A cancer cell from a smear of the pericardial fluid withdrawn on October 23 (Shorr's stain).  $\times 1650$ .

some seeding of tumor as well as a confluent lobular pneumonia and chronic passive congestion. Microscopic examination of all these tissues showed invasion by squamous cell carcinomatous tissue with a disorderly pattern. The neoplasm, which showed a slight tendency toward keratinization, contained cells of varying degrees of anaplasia and degeneration. The inner surface of the cavity was found to be composed of wildly growing neoplastic epithelium. The lymphatics, including those of the esophagus, contained neoplastic emboli. No metastases were found in the brain,

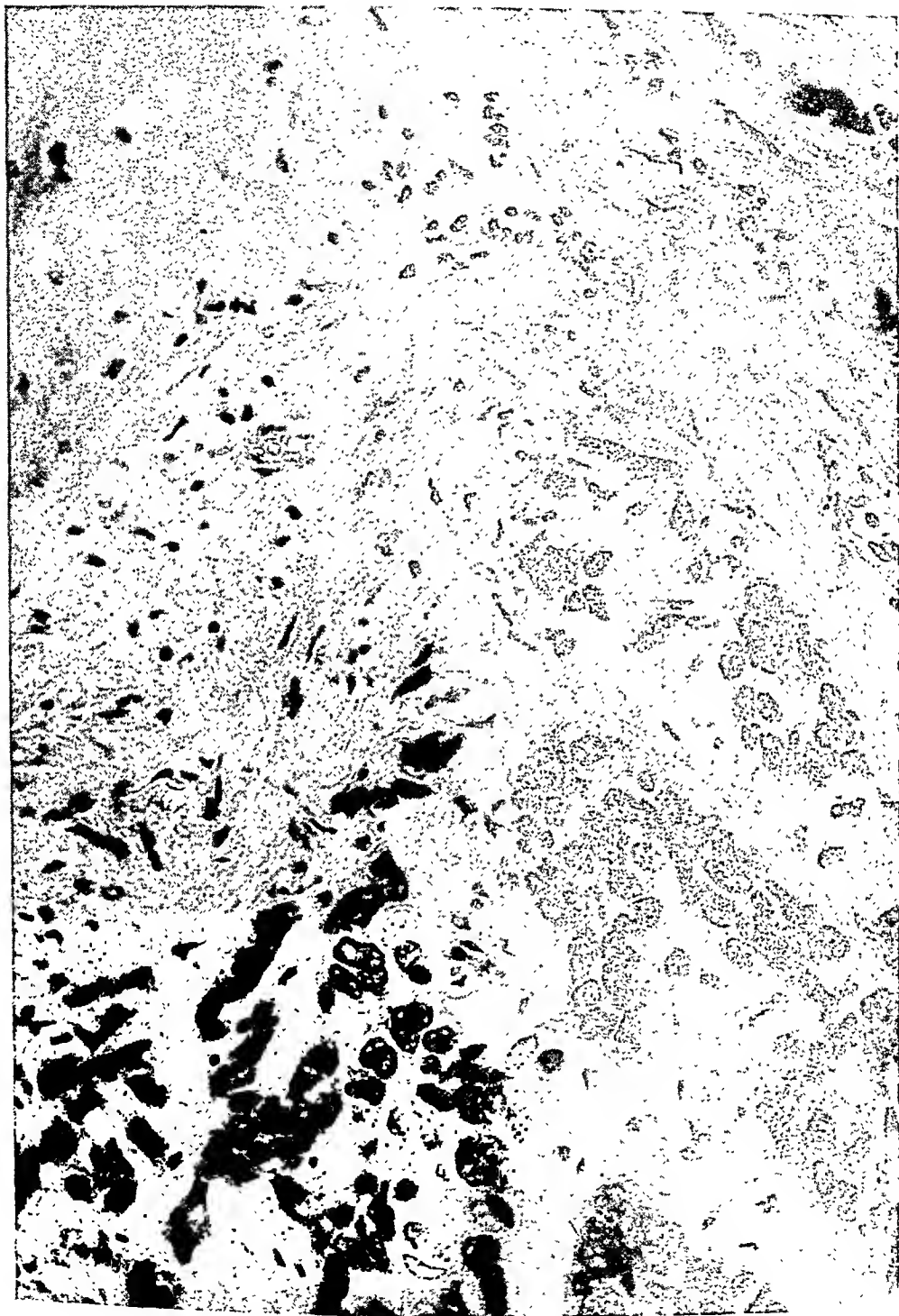


FIG. 6. A section of the tumor taken at autopsy from its origin in the right upper lobe (hematoxylin-eosin).  $\times 375$ .

and the neurological findings were never explained. There was chronic passive congestion of the liver.

The anatomical diagnoses were: 1. Bronchogenic carcinoma, squamous cell type, at junction of the right main bronchus and right upper bronchus with cavitation of right upper lobe and metastases to the mediastinal lymph nodes, pleura, pericardium, and esophagus. 2. Pericarditis, adhesive, due to diffuse carcinomatosis. 3. Obstruction, mechanical, of the superior vena cava by pericardial carcinomatosis. 4. Lobular pneumonia, acute, of the lower lobes of the lungs. 5. Congestion, acute and chronic of the lungs. 6. Hydrothorax, massive, bilateral. 7. Chronic passive congestion of the liver, moderate (figures 6 and 7).



FIG. 7. The contents of the thoracic cavity, posterior view, showing the primary lesion in the right upper lobe bronchus, the cavity distal to the tumor, metastatic tumor in the lymph nodes, and metastatic tumor in the heart and pericardium with almost complete obliteration of the pericardial space.

## COMMENT

The current increasing interest in simple, accurate, cytological technics for the diagnosis of malignancy that has been stimulated by the work of Papanicolaou and Traut,<sup>8,9</sup> Meigs,<sup>10</sup> Herbut and Clerf,<sup>11</sup> and others, has presented the clinician with a valuable tool. The technic used here differs from that used by the workers above, in that Shorr's stain is a single stain and the staining of the nuclei is accomplished not by the traditional hematoxylin but by the action of a single mixture of acid dyes. This gives a nuclear stain that is much more delicate than hematoxylin and shows nuclear detail to advantage. Color contrast is good and allows the investigator to pick out atypical cells and nuclei easily with low power lenses. The disadvantage of poor staining on thick smears or in the presence of very viscid mucus, is overcome by experience in spreading the smears, by longer fixation, and by making multiple smears, usually five of each specimen. Furthermore, the method does not require extensive laboratory facilities. It saves time in staining and mounting, reducing these procedures to approximately five minutes.

So useful a supplementary tool as the smear technic may be invaluable in cases such as the one just presented where, until the sputum was examined, tuberculosis and infected pulmonary cyst were the most strongly considered diagnoses because of the roentgen-ray findings and the negative bronchoscopy. Furthermore, the exact etiology of the pericardial effusion would not otherwise have been demonstrated until necropsy. It must be remembered, however, although there is as yet no substitute for biopsy, that at times roentgen-ray may be misleading, bronchoscopy inconclusive, and biopsy unobtainable. As a result the smear technic is the only diagnostic aid available.

The reasons for the infrequency of a definite antemortem diagnosis of metastatic tumor of the heart and pericardium are two-fold: (1) Biopsy of the myocardium or pericardium is not a practical procedure. One is therefore reduced to the examination of exfoliated cells in aspirated pericardial fluid. These cells may be studied by a number of methods; the most frequently used are either the examination of stained sections of fixed embedded blocks of the cellular sediment of the fluid or stained smears of the sediment made by technics such as that described above. The relative accuracy of cell blocks and smears is not yet settled<sup>5,9,12,13</sup> though we follow Papanicolaou in preferring the latter. In either case, one is deprived of the opportunity of examining by histological methods large masses of cells in their relationships to associated structures, but must depend upon the cytological characteristics of a relatively few detached cells for an evaluation of the pathological processes involved. The identification of malignant cells without the usual criteria of the tissue pathologist may therefore be difficult, and diagnostic accuracy will vary, not only with the method used but with the investigator.

(2) Clinical signs of pericardial disease are often absent or overlooked in those patients with known or suspected cancer of other organs who prove at autopsy to have cardiac metastases. Even when an attempt is made to study patients with both cardiac and neoplastic disease, the amount of pericardial fluid may be too small to detect by physical examination or roentgen-ray. For example, Scott and Garvin<sup>1</sup> in 118 cases of metastatic tumor of the heart and pericardium found involvement of the pericardium in 83 cases (70 per cent) at au-



topsy. Despite the high percentage of pericardial involvement, in only 29 cases (22 per cent) was there present acute pericardial disease that might theoretically have led to the detection during life of metastasis by a method such as ours. Similar findings are seen in the reports of Heniger,<sup>4</sup> Yater,<sup>14</sup> Helwig,<sup>15</sup> Pallia and Gogol<sup>16</sup> and others. Nevertheless, the finding of pericardial effusion is an important diagnostic sign and it would therefore appear advisable to scrutinize all cases of malignancy with any cardiac or pulmonary symptoms more critically and to utilize more carefully the cytological technics at hand.

### SUMMARY

A case of bronchogenic carcinoma with metastases to the pericardium in which neoplastic cells were found in the pericardial fluid as well as in the sputum by wet films stained with Shorr's stain has been presented. The possibilities and advantages of this diagnostic technic have been discussed.

The authors wish to express their appreciation of the valuable assistance extended to them in this study by Dr. Arthur W. Wright, Professor of Pathology and Bacteriology, and by Dr. L. W. Gorham, Professor of Medicine in the Albany Medical College.

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## EDITORIAL

### FURTHER REFINEMENT OF LIVER EXTRACTS EFFECTIVE IN PERNICIOUS ANEMIA

THE production of liver extracts which could be administered parenterally to patients with pernicious anemia constituted an important advance in the treatment of this disease. The earlier types of extracts were crude mixtures in which the active substance was present in relatively high dilution. Although the intensive work carried on during the past 15 years has resulted in the production of extracts for therapeutic use of far higher concentration, attempts to isolate the active substance and determine its chemical nature have hitherto been unsuccessful. Such work has been greatly hampered by the lack of any chemical or biological test to assay or even demonstrate the active substance in the fractions being studied. This could be accomplished only by administering the material to untreated patients with pernicious anemia (or a related anemia), and the supply of suitable patients has been entirely inadequate to meet the demand.

There is now evidence suggesting that this lack may have been supplied. As the result of a systematic search for a bacterium which could be used for the microbiological assay of a factor in liver needed for growth in rats, Shorb<sup>1</sup> discovered that *Lactobacillus lactis* Dorner when cultivated in a suitable basal medium fulfilled this need and grew when liver or liver extract was added to the medium. When assays of various commercial liver extracts were carried out by determining the minimum quantity which would support growth, Shorb found that their activity in this respect corresponded directly and very closely to their potency in "units" as determined by therapeutic tests in patients with pernicious anemia. Shorb suggested that this LLD factor may be the therapeutically active principle in the extracts.

This procedure, therefore, seems to offer a valuable practical means of detecting and measuring—at least tentatively—the active substance in various fractions derived from liver extracts. Rickes et al.<sup>2</sup> have utilized this procedure in their attempts further to concentrate and isolate the active substance in these extracts.

These investigators<sup>2</sup> have recently reported obtaining in minute amounts a highly active crystalline substance in the form of small red needles, which they have tentatively designated as vitamin B<sub>12</sub>, a term which is noncommittal as to its chemical structure and biological and therapeutic significance. Shorb<sup>3</sup> found that 0.000013 micrograms per ml. (1.3 parts per 100,000,000,000) sufficed to produce half maximal growth of *L. lactis* in a 23 hour growth period. With respect to weight it was 11,000 times as potent as an

<sup>1</sup> SHORB, M. S.: Unidentified growth factors for *Lactobacillus lactis* in refined liver extracts, Jr. Biol. Chem., 1947, clxix, 455-456.

<sup>2</sup> RICKES, E. L., et al.: Crystalline vitamin B<sub>12</sub>, Science, 1948, cvii, 396-397.

<sup>3</sup> SHORB, M. S.: Activity of vitamin B<sub>12</sub> for the growth of *Lactobacillus lactis*, Science, 1948, cvii, 397-398.

arbitrarily selected standard liver extract. Shorb believes that it is "either wholly or partly responsible for the LLD growth activity observed for liver extracts."

West<sup>4</sup> has reported the immediate results obtained by administering vitamin B<sub>12</sub> to three patients with pernicious anemia in relapse in single doses of 3, 6, and 150 micrograms respectively. In all three a positive hematological response was obtained. (The response appears excellent for the larger dose but suboptimal for the smaller ones.) On the basis of these observations and microbiological assays, Rickes et al. estimated that 1 microgram of vitamin B<sub>12</sub> corresponds in potency approximately to 1 U.S.P. unit of liver extract.

The therapeutic effectiveness of vitamin B<sub>12</sub> has been confirmed on a limited scale by other observers. Spies et al.<sup>5</sup> treated two cases of pernicious anemia, two of nutritional macrocytic anemia and one of nontropical sprue; and two cases of tropical sprue in Havana<sup>6</sup> with single doses of 6 or 8 micrograms (one patient with pernicious anemia received 15 micrograms). In all seven cases there was a well marked reticulocyte crisis and a significant rise in hemoglobin and red cell count during a period of observation of 10 or 14 days. There was also a marked subjective improvement evident by the third to the fifth day. There was an increased feeling of well being, greater strength and vigor and mental alertness, and relief of the burning and soreness in the mouth. There was also some improvement of the diarrhea in the cases of sprue.

Spies et al.<sup>7</sup> have also reported similar results in the treatment of five cases of tropical sprue in Puerto Rico. One patient showed little or no response to a single dose of 4 micrograms but later responded well to a folic acid preparation. The other four after an initial dose of 10 to 25 micrograms showed a well marked hematological response together with clinical improvement, but they tended to relapse after about three weeks. The administration of second and third doses of 25 micrograms at such intervals was followed by a sharp peak in the reticulocyte count and by further hematological and clinical improvement which was well maintained in the three cases receiving three such doses. Spies estimated that a single dose of 100 micrograms would be required to get a maximum hematological response in severely ill patients. This corresponds approximately in potency to the amount of liver extract commonly administered during the first week of intensive treatment to patients severely ill with pernicious anemia.

The response of the neurological disturbances in patients with pernicious anemia to vitamin B<sub>12</sub> is of great theoretical as well as practical interest. As

<sup>4</sup> WEST, R.: Activity of vitamin B<sub>12</sub> in Addisonian pernicious anemia, *Science*, 1948, cvii, 398.

<sup>5</sup> SPIES, T. D., et al.: Observations on the antianemic properties of vitamin B<sub>12</sub>, *South. Med. Jr.*, 1948, xli, 522-523.

<sup>6</sup> SPIES, T. D., et al.: Observations on the hemopoietic response of persons with tropical sprue to vitamin B<sub>12</sub>, *South. Med. Jr.*, 1948, xli, 523-525.

<sup>7</sup> SPIES, T. D., and SUAREZ, R. M.: Response of tropical sprue to vitamin B<sub>12</sub>, *Blood*, 1948, iii, 1213-1220.

is well known, the lack of parallelism between the severity of the anemia and the neurological degenerations and the relative resistance of the latter to treatment have led to the suggestion that these disturbances result from different deficiencies. The view that the substances which are deficient are different, or at least that the mechanisms for maintaining the integrity of the two tissues are different, is supported by recent experiences with pteroylglutamic (folic) acid. Although the latter usually induces an excellent hematological remission and maintains the blood at essentially normal levels, at least for several months, it has failed completely to control the neurological disturbances. There is even some suggestive evidence that in large doses it may be positively harmful.<sup>8</sup>

The evidence now available, although scanty, indicates that vitamin B<sub>12</sub> is effective in controlling the neurological disturbances as well as the anemia. Spies et al.<sup>5,9</sup> reported "remarkable improvement" subjectively in the neurological disturbances of three cases of pernicious anemia given a single injection of 15 micrograms, with relief of pain, tingling, numbness and stiffness, and increased ability to walk. In one patient there was substantial improvement in the physical signs also. Berk et al.<sup>10</sup> have also reported marked subjective and objective improvement in the neurological disturbances in a patient in severe relapse while on inadequate treatment with pteroylglutamic acid, which had been substituted for liver extract because of severe allergic reactions to the latter. After eight daily doses of 5 micrograms had resulted in marked improvement, treatment was stopped, but within a week a regression occurred. This was again controlled promptly and further improvement initiated by resumption of treatment (5 micrograms three times a week). It is interesting that no allergic reaction occurred to these injections, although the patient still reacted strongly to ordinary liver extracts.

This evidence, although obviously scanty, is so clear cut that it strongly suggests that a deficiency of vitamin B<sub>12</sub> "is closely related to the natural origin of both the blood and the nervous changes."<sup>10</sup> A deficiency of pteroylglutamic acid would appear to play at most a subsidiary rôle in the pathogenesis of the disease as a whole.

The chemical structure of vitamin B<sub>12</sub> has not been reported. The only evidence that it is a specific individual chemical compound, aside from its extraordinary potency, is its isolation in characteristic crystalline form. The mechanism of its action in the body and its relation to other hematopoietic principles are not known, but its isolation marks a major advance and an essential preliminary step toward the elucidation of these problems. The need of vitamin B<sub>12</sub> as a growth factor (LLD factor) for certain bacteria

<sup>8</sup> Ross, J. F., et al.: The development and progression of subacute combined degeneration of the spinal cord in patients with pernicious anemia treated with synthetic pteroylglutamic (folic) acid, *Blood*, 1948, iii, 68-90.

<sup>9</sup> SPIES, T. D., et al.: The association between gastric achlorhydria and subacute combined degeneration of the spinal cord, *Postgrad. Med.*, 1948, iv, 89-95.

<sup>10</sup> BERK, L., et al.: Effectiveness of vitamin B<sub>12</sub> in combined system disease, *New England Jr. Med.*, 1948, ccxxxix, 328-330.

suggests that it plays a more fundamental rôle in the physiology of living organisms than merely as a preventive of pernicious anemia.

From the practical standpoint, vitamin B<sub>12</sub> has thus far been obtained only in minute amounts, and it is available only for experimental purposes and on a regrettably small scale. There is no evidence, however, and no good reason to anticipate that the therapeutic results obtained with it can not be duplicated by adequate doses of liver extracts. Neither pteroylglutamic acid nor any other material now available is an effective substitute for liver extract in the treatment of pernicious anemia.

P. W. C.

## REVIEWS

*The Natural History of Disease.* 2nd Ed. By JOHN A. RYLE, M.A., M.D., F.R.C.P. 484 pages; 14.5 × 22.5 cm. Oxford University Press, London, New York. 1948. Price, \$7.50.

Professor John Ryle is one of the giants in English Medicine. Formerly Professor of Medicine in the University of Cambridge, he was called to the bedside of King George V in consultation. He subsequently declined a knighthood. As consulting physician to Guy's Hospital, he had a large London practice, which he relinquished some years ago to accept the newly created Professorship of Social Medicine at Oxford.

His book consists of a collection of 37 papers written during the last 25 years. Three have been added since the first edition in 1936. The topics discussed are varied. Two chapters are entirely philosophical—the Physician as Naturalist, and the Hippocratic Ideal. Some, though mainly philosophical, have decided and valuable clinical bearing—Prognosis, On Nosophobia, and Diathesis or Variation and Disease in Man. In the many purely clinical papers the main territories occupied are gastrointestinal and cardiovascular symptoms and diseases, and pyogenic infections. Many of these chapters deal with subjects of great practical importance, yet often inadequately covered by standard textbooks and clinical instructors alike—the Clinical Study of Pain, the Study of Symptoms, Observations on Colonic Pain, On Examining the Rectum, the Radial Pulse, and many others. Helpful accounts of common disorders form the subjects for other chapters, and include The Natural History of Duodenal Ulcer, Anorexia, Chronic Diarrhea and Some Alarming Seizures. The chapter on the Prognosis and Treatment of Lobar Pneumonia, despite the great advances made in this subject, has been left as it appeared in the former edition; because, in the author's words, "it would be a pity if the student were to lose interest in the prognosis and difficult judgments which it requires," and "the types of judgment requisite for assessing new methods is the same."

The book is written in simple, direct style, and is therefore easy to read. It is not a textbook in any sense. It makes no pretence to give a complete account of, or even to be up to date in the knowledge of many of the subjects discussed. It consists literally of pages from the notebook of a great clinician and a widely acclaimed teacher—"gleanings from the current experience of a general physician." The main concern of the author is the symptomatology and portraiture of disease, and little mention is made of accessory aids to diagnosis. To that breed of physicians, therefore, whose interest is focussed more on the laboratory sheet than on the patient, this book will make weary, stale and flat, though not unprofitable, reading.

In this day and country, with clinical instruction too often in the hands of young and callow physicians, whose experience is necessarily limited and judgment unformed, these pages should be of particular value to the student and interne. Even the established physician (although as he reads he may be impatient at much that appears naïve or repetitious) would do well to refresh himself with the principles and value of careful, bedside observation, so well set out in these chapters, and so often overlooked in today's super-scientific enthusiasm. "No amount of scientific training or technical ability can supply those qualities of naturalist and of humanist, without which the good physician can never fully earn his title."

H. J. L. M.

*Occupational Medicine and Industrial Hygiene.* By RUTHERFORD T. JOHNSTONE, A.B., M.D., Consultant in Industrial Health, Los Angeles. 604 pages; 17 × 25 cm. C. V. Mosby Co., St. Louis. 1948. Price, \$10.00.

This excellent book begins with a section covering miscellaneous subjects, including a short historical introduction to industrial medicine. A chapter consists of definitions and of tabulations of the compensation laws of various states. Following this there is a comprehensive discussion of the functions of an industrial surgeon with the objectives to be obtained. Next, a tabulation of laboratory procedures in the diagnosis of occupational poisoning, with normal findings when available; a very valuable summary.

Approximately one-fourth of the book is devoted to the various toxic agents used in industry. These have been given adequate consideration. The author emphasizes those which have such use by the laity that the general physician is apt to come across occasional examples of poisoning in his practice, such as methyl alcohol, carbon monoxide, carbon tetrachloride, methyl chloride and sulfur dioxide. Carbon monoxide poisoning is covered at some length, not only the usual body changes following exposure, but also the more controversial aspects as to the possibility of permanent sequelae in the central nervous system and in the heart.

The heavy metals are considered in considerable detail. In discussing lead poisoning the author is quite emphatic in stressing the necessity for accurate diagnosis, and expresses the belief that in industry many individuals are diagnosed as having lead poisoning upon insufficient grounds. Here again he points out the controversial aspects, particularly whether lead can be fixed in a stable form in the skeletal system. This was the conception of Aub, Fairhall, Minot and Reznikoff, as published in 1926. Since then the dietary treatment has been based on the use of high calcium diets to "fix the lead" and low calcium intake to "delead." The author quotes certain investigators whose work indicates that this is doubtful and indeed that a high calcium diet to deposit lead in the bones may have serious consequences.

Another one-fourth of the book takes up the changes produced by the inhalation of the various dusts including silicosis, anthrosilicosis, asbestosis, etc. as well as a so-called inert dust. These chapters are well illustrated, and afford a compact and yet informative review of this important subject. There is included a short but pertinent chapter devoted to the consideration of tuberculosis and pneumonia in industry.

The occupational dermatoses are dealt with rather briefly with emphasis given chiefly to diagnostic criteria. There are well illustrated chapters on various phases of industrial hygiene.

An appendix tabulates the numerous chemicals contained in trade-name products used in the various industries as well as by the laity. This table is especially valuable as affording information which cannot be obtained from the labels on the products themselves nor from the publications of the manufacturer.

As stated in the beginning, this is an excellent book. It seems primarily intended for the use of plant physicians and other specialists in industrial medicine. However, the informative discussions of the commoner exposures, and particularly the references appended at the end of each chapter, would make this book also serve as a quick reference for the doctor who is only occasionally interested in industrial medical problems.

G. C. L.

*Psychiatry for the Pediatrician.* By HALE F. SHIRLEY, M.D. 442 pages; 16 × 24 cm. The Commonwealth Fund, New York. 1948. Price, \$4.50.

The very first chapter in this book introduces the general practitioner and pediatrician to many old patients. There again is Johnny, who objects to examination;

Elsie, who doesn't want to eat; James, wailing to go home and his mother who vociferously objects to waiting. And Mrs. Brown who wants to know how she can make Nancy take her afternoon nap, as well as Mrs. Black who wants to know what the doctor is going to do "next" about Henry's bed-wetting. Admittedly they are all familiar characters and problems, and here Dr. Shirley lays the pattern for subsequent discussion. The book throughout is kept at a level of presentation that is commensurate with the practitioner's knowledge of child psychiatry. As stated in the preface, it is devoid of "psychiatric verbiage," and as an aid to a more complete understanding, a short glossary has been appended. The departures made from common every day behavior problems into true psychopathological problems are infrequent and only serve to provide the practitioner with some norm as to his limitation.

There has been an increasing demand made upon the general practitioner and pediatrician to help parents emerge from the morass of confusing psychological advice that has been appearing in current lay publications. This book seems to the reviewer to be a timely publication in providing the physician with an understanding of these problems. Indeed more discussion should be allotted to the environmental factors, such as "movies," "comics," and radio with presentation of prevailing views other than the author's as to their influence upon child development.

An entire chapter is given over to the discussion of "Sexual Factors and Problems," and the discussion is on a sane, common sense level devoid of the almost pathological significance that many psychiatrists attach to this drive.

J. E. B.

*Diabetes Mellitus in General Practice.* By ARTHUR R. COLWELL, M.D. 350 pages; 14.5 × 21 cm. The Year Book Publishers, Inc., Chicago. 1947. Price, \$5.25.

Dr. Colwell has written an interesting monograph on the treatment of diabetes. The qualification of the title by the words "In General Practice" is somewhat misleading, as the presentation is probably too detailed to appeal to the average general practitioner. The book is more suited to the use of the internist.

The subject matter is clearly presented, the general plan of treatment is good, and discussions of emergencies and complications are satisfactory. Usefulness of the book could be increased by inclusion of a large number of sample diets, as calculation of the dietary prescription is for most physicians a difficult problem.

The reviewer, who is diabetic, believes that the description of the technic of insulin administration is too complicated. He is also aghast at the suggestion that diabetes in a pregnant woman is an indication for abortion if the husband's family history is found to be positive.

With these few exceptions, "Diabetes Mellitus in General Practice" may be recommended as a satisfactory guide for the management of the diabetic patient.

T. N. C.

*The Diagnosis and Treatment of Menstrual Disorders in Sterility.* 2nd Ed. By CHARLES MAZER and S. LEON ISRAEL. 570 pages; 16.5 × 24 cm. Paul B. Hoeber, Inc., New York, N. Y. 1946. Price, \$7.50.

This rewritten second edition, like the first, has been designed to fulfill the need of the general practitioner who is interested primarily in the practical aspects of these subjects. New developments in the field of endocrinology and the extensive clinical experience of the authors in dealing with problems of sterility made revision necessary. All but four chapters have been largely rewritten. Some have been considerably enlarged.

The book begins with a detailed description of the anatomy and physiology of the pituitary gland and the ovary. There is included in the first part a discussion of anti-



hormone effects. Also, there is an outline of the relative potency of the numerous estrogens in terms of international and rat units per milligram and the most effective methods of administration of these products. Following this there are chapters on puberty in the female, the normal menstrual cycle, and the hormone balance of the normal menstrual cycle. These add nothing new.

Dysmenorrhea, premenstrual tension, migraine, breast hyperplasia, mittelschmerz, and vicarious menstruation are dealt with in a rather elementary way, but the authors stress the essential known facts regarding the etiology and treatment of these conditions. Amenorrhea, functional bleeding, and sterility are discussed in great detail and the chapters dealing with these subjects are excellent. Methods of diagnosis, office procedures and treatment are given in detail.

The chapter on male infertility is by Dr. Charles W. Charney. It has been completely rewritten and covers the subject thoroughly. Toxemias of pregnancy and the Rh factor are discussed very briefly and might just as well have been omitted. At the end of the book there is a very excellent detailed list of the various commercially available standardized products. The book includes many excellent photographs and microphotographs.

Throughout, one cannot help but be impressed by the sincerity of the authors in their effort to stress proved, modern methods of treatment for these clinically related conditions. This book fills a gap between the ultra-scientific papers on endocrinological subjects and the "commercial propaganda" regarding the clinical use of hormones. The book is well worth reading.

J. C. D.

#### BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*A. M. A. Interns' Manual.* 201 pages; 18.5 × 11 cm. 1948. W. B. Saunders Company, Philadelphia. Price, \$2.25.

*Ärztliche Rheokardiographie.* By WOLFGANG HOLZER and KURT POLZER. 141 pages; 24 × 17 cm. (paper bound). 1948. Verlag Wilhelm Maudrich, Vienna, Austria; imported by Grune & Stratton, New York. Price, \$3.00.

*Die Stumpfen Bauchverletzungen ihre Erkennung und Behandlung.* By DR. ADALBERT SLANY. 137 pages; 23 × 15.5 cm. (paper bound). 1948. Verlag Wilhelm Maudrich, Vienna, Austria; imported by Grune & Stratton, New York. Price, \$3.50.

*Die Vegetativen Anfälle des Herzens.* By KURT POLZER and WALTER SCHOBER. 88 pages, 23 × 15.5 cm. (paper bound). 1948. Verlag Wilhelm Maudrich, Vienna, Austria; imported by Grune & Stratton, New York. Price, \$2.50.

*Human Biochemistry.* 2nd ed. By ISRAEL S. KLEINER, Ph.D., Professor of Biochemistry and Director of the Department of Physiology and Biochemistry, New York Medical College, Flower and Fifth Avenue Hospitals, etc. 649 pages; 25 × 17 cm. 1948. The C. V. Mosby Company, Saint Louis. Price, \$7.00.

*Liver Injury: Transactions of the Seventh Conference, January 15 and 16, 1948, New York, N. Y.* Edited by F. W. HOFFBAUER, M.D., Department of Medicine, University of Minnesota. 95 pages; 23 × 16 cm. (looseleaf, paper bound). 1948. Josiah Macy, Jr. Foundation, New York. Price, \$1.50.

- Malignant Disease and Its Treatment by Radium.* Volume I. 2nd Ed. By SIR STANFORD CADE, K.B.E., C.B., F.R.C.S., M.R.C.P., Surgeon, Westminster Hospital, Mount Vernon Hospital and Radium Institute, etc.; with a Foreword by SIR ERNEST ROCK CARLING, F.R.C.P., F.R.C.S., F.F.R., Consulting Surgeon and Vice-President, Westminster Hospital. 383 pages; 23.5 × 16 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$12.50.
- Management of Common Gastro-intestinal Diseases.* Edited by THOMAS A. JOHNSON. Contributors: A. H. AARON, ALBERT F. R. ANDRESEN, Z. T. BERCOVITZ, J. EDWARD BERK, OLOV BLUMQUIST, E. N. COLLINS, BURRILL B. CROHN, E. GARCIA, M. I. GROSSMAN, W. PAUL HAVENS, JR., A. C. IVY, SARA M. JORDAN, JOSEPH B. KIRSNER, N. HABALUYAS KUO, ELMER MILCH, WALTER LINCOLN PALMER, RUDOLF SCHINDLER, CO TUI, HENRY J. TUMEN, EDWARD WEISS, and HARRY YARNIS. 280 pages; 24 × 16 cm. 1948. J. B. Lippincott Company, Philadelphia. Price, \$7.00.
- Methods in Medical Research.* Volume I. VAN R. POTTER, Editor-in-Chief. Assay of Antibiotics, HENRY WELCH, Editor; Circulation—Blood Flow Measurement, HAROLD D. GREEN, Editor; Selected Methods in Gastroenterologic Research, A. C. IVY, Editor; Cellular Respiration, VAN R. POTTER, Editor. 372 pages; 23.5 × 15.5 cm. 1948. Year Book Publishers, Inc., Chicago. Price, \$8.00.
- Pediatrics and the Emotional Needs of the Child, as Discussed by Pediatricians and Psychiatrists at Hershey, Pennsylvania, March 6-8, 1947.* Edited by HELEN L. WITMER. 180 pages; 23 × 15.5 cm. (paper bound). 1948. The Commonwealth Fund, New York. Price, \$1.50.
- Psychiatry in General Practice.* By MELVIN W. THORNER, M.D., D.Sc., Assistant Professor of Neurology, The Graduate School of Medicine, University of Pennsylvania. 659 pages; 24 × 16 cm. 1948. W. B. Saunders Company, Philadelphia. Price, \$8.00.
- The RH Blood Groups and Their Clinical Effects—Medical Research Council Memorandum No. 19.* By P. L. MOLLISON, A. E. MOURANT and R. R. RACE. 74 pages; 24.5 × 15 cm. (paper bound). 1948. His Majesty's Stationery Office, London. Price, 1s. 6d. net.
- The Surgery of Abdominal Hernia.* By GEORGE B. MAIR, M.D., F.R.F.P.S.G., F.R.C.S.E., Surgeon, Law Junction Hospital, Lanarkshire, etc. 408 pages; 22 × 14.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$7.00.
- The Thyroid and Its Diseases.* 2nd Ed. By J. H. MEANS, M.D., Jackson Professor of Clinical Medicine, Harvard University, etc. From the Thyroid Clinic of the Massachusetts General Hospital. 571 pages; 23.5 × 15.5 cm. 1948. J. B. Lippincott Company, Philadelphia. Price, \$12.00.
- Über Neurome und Neurofibromatose, Nach Untersuchungen am Menschlichen Magendarmschlauch.* By F. FEYRTER, O. Professor der Pathologie, Georg Hanusch-Krankenhaus der Wiener Gebietskrankenkasse für Arbeiter und Angestellte, Wien XIV. 125 pages; 24.5 × 17.5 cm. (paper bound). 1948. Verlag Wilhelm Maudrich, Vienna, Austria; imported by Grune & Stratton, New York. Price, \$3.50.
- Viral and Rickettsial Infections of Man.* Edited by THOMAS M. RIVERS, M.D., Director of the Hospital, The Rockefeller Institute for Medical Research. 587 pages; 26.5 × 18 cm. 1948. J. B. Lippincott Company, Philadelphia. Price, \$5.00.

# COLLEGE NEWS NOTES

## MEETING OF THE BOARD OF REGENTS

The Board of Regents met in Philadelphia on November 7, 1948. The minutes of this meeting will be published in a later issue of the ANNALS OF INTERNAL MEDICINE.

The following candidates were elected as Fellows or Associates of the American College of Physicians.

### *Fellows*

Edwin Bennett Astwood .....	Boston, Mass.
Oscar Auerbach .....	Staten Island, N. Y. (V. A.)
Noyes Latham Avery, Jr. ....	Grand Rapids, Mich.
Joseph Ballinger .....	New York, N. Y.
Charles Scott Barker .....	Montreal, Que., Can.
Joseph Michael Barker .....	Washington, D. C.
William Bennett Bean .....	Iowa City, Iowa
Milton Dietrick Bosse .....	Pitcairn, Pa.
J(ames) Russell Brink .....	Grand Rapids, Mich.
Mortimer Jacob Cantor .....	Brooklyn, N. Y.
David Cayer .....	Winston-Salem, N. C.
Don Wilton Chapman .....	Houston, Tex.
Aaron Cohen .....	Brooklyn, N. Y.
Peter Diacounis Comanduras .....	Arlington, Va.
William Dean Coventry .....	Duluth, Minn.
William Llewellyn Cover .....	San Bernardino, Calif.
Joseph Henry Delaney, Sr. ....	Spokane, Wash.
Vincent Joseph Derbes .....	New Orleans, La.
Nicholas John DiGregorio .....	Brooklyn, N. Y.
Joseph Doupe .....	Winnipeg, Man., Can.
Earl Foster Evans .....	M. C., U. S. Navy
Neil Feeney .....	Montreal, Que., Can.
Marcus Abraham Feinstein .....	New York, N. Y.
Elmer Friedland .....	Buffalo, N. Y.
Arthur Joseph Geiger .....	New Haven, Conn.
Robert Hardin Hackler, Jr. ....	Washington, N. C.
Oscar Carl Edvard Hansen-Pruss .....	Durham, N. C.
Hilbert Lawrence Harris .....	Syracuse, N. Y.
Peter Andrew Herbut .....	Philadelphia, Pa.
Lawrence Wheelock Holden .....	Boulder, Colo.
Joseph Carlino Indelicato .....	Brooklyn, N. Y.
Lewis Edward January .....	Iowa City, Iowa
Sture A. M. Johnson .....	Madison, Wis.
William Henry Kammerer .....	New York, N. Y.
Max Joseph Klainer .....	Stoneham, Mass.
Yale Knefland, Jr. ....	New York, N. Y.
Israel Kopp .....	Boston, Mass.

Sprul Tul Lauffer .....	Halifax, N. S.
Edward James Lefebber .....	Galveston, Tex.
William Cohn Levin .....	Galveston, Tex.
Frederic Henry Lewey .....	Philadelphia, Pa.
Victor Filler Lief .....	Far Rockaway, N. Y.
Louis Robert Limarzi .....	Chicago, Ill.
Wallace William Lindahl .....	Seattle, Wash.
Eugene Leonard Lozner .....	Syracuse, N. Y.
Mischa J. Lustok .....	Milwaukee, Wis.
Paul Budd Magnuson .....	Washington, D. C. (V. A.)
Ronald John McNamara .....	Charleston, W. Va.
Theodore Herzl Mendell, Sr. ....	Philadelphia, Pa.
Edward Sadler Mills .....	Montreal, Que., Can.
Samuel Mirsky .....	Ottawa, Ont., Can.
Franklin David Murphy .....	Kansas City, Kan.
Don Edwin Nolan .....	Dayton, Ohio (V. A.)
Oscar Armand Palatucci .....	New York, N. Y.
Jerome Thomas Paul .....	Wilmette, Ill.
William Nottingham Powell .....	Temple, Tex.
Samuel Jeremiah Prigal .....	New York, N. Y.
Roscoe LeRoy Pullen .....	Seattle, Wash.
Joseph George Ruston, Sr. ....	Glendale, Calif.
Clement Franklin St. John .....	M. C., U. S. Army
Bertram Julian Sanger .....	New York, N. Y.
Edmund Lester Shlevin .....	Brooklyn, N. Y.
Norman Richard Shulack .....	Brooklyn, N. Y.
Leslie Benjamin Smith .....	Phoenix, Ariz.
Richard Henry Smith .....	USPHS
Mayo Hamilton Soley .....	Iowa City, Iowa
Robert Folger Solley .....	Palisades, N. Y.
Charles Lewis Spurr .....	Houston, Tex.
Irwin Daniel Stein .....	Tuckahoe, N. Y.
Robert Harold Talkov .....	Boston, Mass.
Lawrence Jay Thomas .....	Washington, D. C.
Samuel Waldman .....	Brooklyn, N. Y.
Joseph James Wallace .....	Washington, D. C.
Otis Sumter Warr .....	Memphis, Tenn.
Earle Macbeth Watson .....	London, Ont., Can.
Joseph Cook Watts .....	Bayside, N. Y.
Frederick Renfroe Weedon .....	Jamestown, N. Y.
Samuel Joseph Weinberg .....	Los Angeles, Calif.
William Hays Windley .....	Newport News, Va.
George Alexander Zindler .....	Battle Creek, Mich.

*Associates*

Emanuel M. Abrahamson .....	New York, N. Y.
Alan Louis Abrams .....	San Francisco, Calif.
Harry Nils Akesson .....	Oakland, Calif.

John Bellows Alsever .....	USPHS
Leighton Lars Anderson .....	Denver, Colo.
Maurice Joseph Ansfeld .....	Milwaukee, Wis.
Prince Patanilla Barker .....	Tuskegee, Ala. (V. A.)
Biagio Battaglia .....	Brooklyn, N. Y.
Frank Louis Bauer .....	M. C., U. S. Army
Robert H. Beck .....	Huntingdon, Pa.
Paul Lincoln Bedinger .....	Evanston, Ill.
Virginia Patterson Beelar .....	Washington, D. C.
Nathaniel G. Berk .....	Philadelphia, Pa.
John William Berry .....	Denver, Colo.
Albert Alfred Biederman .....	M. C., U. S. Army
Olov Albert Blomquist .....	Los Angeles, Calif.
Albert Murton Bond .....	Melrose, Mass.
Katherine Helen Borkovich .....	Baltimore, Md.
Edward Thurston Brading .....	Johnson City, Tenn.
Thomas Wayne Brewer .....	Houston, Tex.
William Charles Bridges .....	Seattle, Wash.
Francis Jack Brown .....	Decatur, Ill.
Robert Hamilton Browning .....	Oberlin, Ohio
Walter Albert Brussock .....	Milwaukee, Wis.
John Myles Buchanan .....	Huntington Park, Calif. (V. A.)
Philip Larkin Byers .....	Kansas City, Mo.
Orlando Canizares .....	New York, N. Y.
David Turner Carr .....	Rochester, Minn.
William Robert Carson .....	Potsdam, N. Y.
William Arnold Christian .....	Chicago, Ill. (V. A.)
Elmer Fredolph Christopherson .....	Vancouver, B. C., Can.
John Mark Church .....	Fort Worth, Tex.
Edward Alexander Cleve .....	M. C., U. S. Army
Archibald Clinton Cohen .....	Butler, Pa. (V. A.)
Isidor Cohn .....	Brooklyn, N. Y.
Ralph Earl Cole .....	Westford, Mass.
Morris Frank Collen .....	Oakland, Calif.
James Robert Colvert .....	Oklahoma City, Okla.
William Leigh Cook, Jr. ....	Pittsburgh, Pa.
Patrick John Valentine Corcoran .....	Evansville, Ind.
Norman Leo Cressy .....	Newington, Conn. (V. A.)
Leo Hermann Crip .....	Pittsburgh, Pa.
James Hawley Currens .....	Boston, Mass.
Quin Bernard DeMarsh .....	Seattle, Wash.
Charles Campbell Derrick .....	Springfield, Mass.
Francis Curtis Dohan .....	Bala-Cynwyd, Pa.
John Newell Edson .....	Brooklyn, N. Y.
Thomas Stilwell Edwards .....	Charlottesville, Va.
Roger Olaf Egeberg .....	Los Angeles, Calif. (V. A.)
William Weborg Engstrom .....	New Haven, Conn.
Fredric Bickel Faust .....	Lansdowne, Pa.
Louis Feldman .....	Chicago, Ill.
Samuel A. Feldman .....	New York, N. Y.
Leonard Elihu Field .....	New York, N. Y.

Morris Fogel .....	Brooklyn, N. Y.
George William Forman .....	St. Joseph, Mo.
John Franklin .....	Norfolk, Va.
Arthur J. Freedman .....	Greensboro, N. C.
Robert John Freedman .....	Alexandria, La. (V. A.)
Rudolph Eric Fremont .....	Staten Island, N. Y. (V. A.)
Robert Friedenbergl .....	Albuquerque, N. M.
Sidney Friedlaender .....	Detroit, Mich.
Joseph Harman Fries .....	Brooklyn, N. Y.
Andrew Bole Fuller .....	Pittsburgh, Pa.
H(enry) Harold Gelfand .....	New York, N. Y.
Alexander Gerber .....	Brooklyn, N. Y.
Horace Craig Gibson .....	M. C., U. S. Army
William Carleton Gibson .....	Edmonton, Alta., Can. (Temporarily in Australia)
James Samuel Glotfelty .....	St. Louis, Mo. (V. A.)
Herman Gold .....	Chester, Pa.
Morris Alan Gold .....	Butte, Mont.
Emanuel Goldberger .....	New York, N. Y.
Mervin Jack Goldman .....	San Francisco, Calif. (V. A.)
Robert Sid Arthur Green .....	Cincinnati, Ohio
Lucien Anthony Gregg .....	Pittsburgh, Pa.
Elizabeth Grimm .....	Madison, Wis.
Marshall Eugene Groover, Jr. ....	M. C., U. S. Army
Stanley Herbert Gumbiner .....	Chicago, Ill.
Robert Calvin Hardin .....	Iowa City, Iowa
Max Harten .....	Brooklyn, N. Y.
Edgar A. Haunz .....	Grand Forks, N. D.
William Isaac Heine .....	Philadelphia, Pa.
Robert Arthur Hettig .....	Houston, Tex.
Ralph Emerson Hibbs .....	Portland, Ore.
Homer Allen Howes .....	Detroit, Mich.
Ferdinand Joseph Henry Hruby .....	Cleveland, Ohio
Leroy Hyde .....	Van Nuys, Calif. (V. A.)
Grover Donald Icenogle .....	Bismarck, N. D.
Harold Melvin Johnson .....	Honolulu, T. H.
Reverdy Hamlin Jones, Jr. ....	Roanoke, Va.
Cheney Cleveland Joseph .....	Baton Rouge, La.
Gustav Mason Kahn .....	M. C., U. S. Navy
Julius Kahn .....	Beverly Hills, Calif.
Aaron Louis Kaminsky .....	M. C., U. S. Army
Milton Kantor .....	Mountain Home, Tenn. (V. A.)
Hyman Mandel Katz .....	Brooklyn, N. Y. (V. A.)
Eugene Maurice Katzin .....	Newark, N. J.
Manuel Kaufman .....	Boston, Mass.
Walter Kempner .....	Durham, N. C.
Winfred Price Killingsworth .....	Port Arthur, Tex.
Friedrich Wilhelm Klemperer .....	Trudeau, N. Y.
Joseph Francis Kuzma .....	Wauwatosa, Wis.

Robert (Evariste) Lachance	Verdun, Que., Can.
Aaron Melchior Lefkovits	Memphis, Tenn. (V. A.)
Jack Jay Levin	Wood, Wis. (V. A.)
Dexter Shirley Levy	Buffalo, N. Y.
Max(well) Peter Lipman	Los Angeles, Calif.
Bernard M. Lipschultz	Dallas, Tex. (V. A.)
Ephraim Theodore Lisansky	Baltimore, Md.
David Littmann	West Medford, Mass. (V. A.)
Harold Joseph Livingston	Brooklyn, N. Y.
William Pierce Logan	Lakeland, Fla.
Robert Stanley Long	Omaha, Nebr.
Leonard Louis Lovshin	Shaker Heights, Ohio
Hope Lowry	Denver, Colo.
Harold Duff Lynch	Evansville, Ind.
Benjamin Harry Lyons	Winnipeg, Man., Can.
Harold Joseph Magnuson	USPHS
Florence Iris Mahoney	Memphis, Tenn. (V. A.)
Philip Wallace Mallory	M. C., U. S. Army
Joseph Pickett McCracken	Durham, N. C.
Clinton Hull McKay	Charlotte, N. C.
Atholl Munro McNabb	Ottawa, Ont., Can.
Donald Lauchlin McNeil	Calgary, Alta., Can.
Joseph Goheen McWilliams	Providence, R. I.
Manson Meads	Winston-Salem, N. C.
Walter Herman Mendel	Memphis, Tenn. (V. A.)
John Kimberly Meneely, Jr.	Albany, N. Y.
Donald Duncan Meyer	Potwin, Kans.
Hyman Miller	Beverly Hills, Calif.
Robert Francis Miller	Portland, Ore.
Clark Herold Millikan	Iowa City, Iowa
Sidney Pearce Mitchell	Palo Alto, Calif.
Maurice Roberts Moore	Norwich, Conn.
Jacob Copple Moscovitch	West Vancouver, B. C., Can.
Harold Krieger Moss	Cincinnati, Ohio
Earnest Eric Muirhead	Dallas, Tex.
Earl I. Mulmed	Tulsa, Okla.
Colin Alexander Munroe	Charlotte, N. C.
David Aaron Nathan	Miami Beach, Fla.
George Loren Norris	Winfield, Kans.
John Wendell Oast, III	Norfolk, Va.
Jacques Olivier	Sherbrooke, Que., Can.
Oscar Charles Olson	Spokane, Wash.
William Emanuel Olson	Fort Meade, S. D. (V. A.)
Elliot Oppenheim	New York, N. Y.
Arthur Hazleton Owens, Jr.	Birmingham, Ala.
Franklin Kittredge Paddock	Pittsfield, Mass.
Jean Peter Papps	Forest Hills, N. Y.
Benjamin Pearlman	Chicago, Ill.
Clarence Coplyn Pearson	Seattle, Wash.
Martin Perlmutter	Brooklyn, N. Y.
John Eric Peterson	Los Angeles, Calif.

David Chester Pewterbaugh .....	York, Pa.
Gerald Irving Pitegoff .....	Hartford, Conn.
William Rady Platt .....	Louisville, Ky.
Theodore Zane Polley .....	Joliet, Ill.
Byron Edward Pollock .....	M. C., U. S. Army
Clifford Porter Powell .....	M. C., U. S. Navy
Curtis Prout .....	Dedham, Mass.
Adolph Post Raab .....	Brooklyn, N. Y.
Carl Hirsch Rabin .....	New Orleans, La.
Linus Edwin Rausch .....	Dayton, Ohio
Jerome Olkin Ravel .....	Austin, Tex.
John Thomas Read .....	Columbus, Ohio
William Earl Redfern .....	Detroit, Mich.
Roy Foster Roberts .....	M. C., U. S. Army
Edward Heinrich Robitzek .....	Staten Island, N. Y.
Jack Morton Rose .....	Houston, Tex.
Reno Rosi .....	Chicago, Ill.
Bernard Daniel Ross .....	Miami, Fla.
William Rottersman .....	North Little Rock, Ark. (V. A.)
Ernest Welton Saward, Jr. ....	Vancouver, Wash.
Harold Scheff .....	St. Louis, Mo.
Isadore Schlamowitz .....	Brooklyn, N. Y.
Edward David Schwartz .....	Cleveland, Ohio
Harold Schwartz .....	Cleveland Heights, Ohio (V. A.)
I(sidor) Richard Schwartz .....	Brooklyn, N. Y.
Nathaniel H. Schwartz .....	Port Chester, N. Y.
David William Scott, Jr. ....	Fredericksburg, Va.
Sydney Selesnick .....	Newington, Conn. (V. A.)
Thomas Richard Shoupe .....	Findlay, Ohio
Warren Kousch Simmons .....	Rhineland, Wis.
Ethan Allen Hitchcock Sims .....	New Haven, Conn.
Joseph Slusky .....	Detroit, Mich.
Harald Aasvald Smedal .....	M. C., U. S. Navy
Donal Ross Sparkman .....	Seattle, Wash.
Paul William Spear .....	Brooklyn, N. Y. (V. A.)
Tobias Stein .....	Boston, Mass. (V. A.)
John Henry Taber .....	M. C., U. S. Army
Alex(ander) Watkins Terrell, Jr. ....	Dallas, Tex.
T(homas) Ewing Thompson, Jr. ....	Pittsburgh, Pa.
Stephen Benedict Thorson .....	Calgary, Alta., Can.
Paul Kinley Tisdale .....	St. Vital, Man., Can.
Charles Robert Tittle, Jr. ....	Glenside, Pa.
George Joseph Train .....	Brooklyn, N. Y.
George Panages Vryonis .....	Alexandria, La. (V. A.)
Ephraim Lionel Wagner .....	Houston, Tex.
Harry C. Wall .....	Kansas City, Mo.
Norman Melvin Wall .....	Pittsburgh, Pa.
David Michael Wayne .....	Fort Meade, S. D. (V. A.)
Frederick Clarence Weber, Jr. ....	Greenwich, Conn.
Charles Randall Welfare .....	Winston-Salem, N. C.



Benjamin Baxter Wells .....	Houston, Tex.
John Henry Wheeler .....	Kansas City, Mo.
J(oseph) Maxwell Williams, Jr. ....	Tampa, Fla.
Norman Eric Williams .....	Daytona Beach, Fla.
Onie Owen Williams .....	Phoenix, Ariz.
Marvin Norman Wincer .....	Buffalo, N. Y.
Jack Walter Wolf .....	Kansas City, Mo.
Harris Lincoln Woodburne .....	Detroit, Mich.
Cyril Thompson Yancey .....	Monroe, La.
Henry A. Zimmerman .....	Cleveland, Ohio
Lynwood Duane Zinn .....	Clarksburg, W. Va.
Irving Herman Zitman .....	Chicago, Ill.

### *Award of Research Fellowships*

The Board of Regents of the College awarded eight Research Fellowships in Medicine for the year beginning July, 1949, to applicants nominated by the Committee on Fellowships and Awards. The Fellowships are designed especially for the benefit of young physicians who are in the early stages of preparation for a teaching and investigative career in medicine. As in past years, there were many applications to be studied by the members of the Committee.

The awards for 1949-1950 were made to the following physicians:

JAMES KILGORE DeVORE, M.D., of Dallas, Tex. A graduate of Central College, Fayette, Mo., in 1943, Dr. DeVore received the M.D. degree from the University of Oklahoma School of Medicine in 1947, and interned at the State of Wisconsin General Hospital, Madison, in 1947-1948. Now a fellow in internal medicine in The Frank E. Bunts Education Institute of the Cleveland Clinic, Dr. DeVore will conduct studies next year with Drs. Irvine H. Page, F.A.C.P., and Arthur C. Corcoran, in the Research Division of the Cleveland Clinic, on the determination of the action of active adrenal steroids in dogs and in patients with hypertension.

STEFAN STANISLAUS FAJANS, M.D., Ann Arbor, Mich. A graduate of the University of Michigan (B.S., 1938; M.D., 1942), Dr. Fajans interned at the Mount Sinai Hospital, New York City, and served as medical officer in the U. S. Army. Returning to Ann Arbor in 1946, he has since held appointments in the University Hospital as research fellow, assistant resident, and resident, in internal medicine. Dr. Fajans' application was granted to enable him to undertake studies with Jerome W. Conn, M.D., F.A.C.P., in the Metabolism Research Unit and the Endocrinology and Metabolism Clinic of the University Hospital, to determine the physiological mechanisms capable of either stimulating or depressing the Islets of Langerhans.

HORACE WILLIAM GERARDE, M.S., M.D., of Rockford, Ill. Dr. Gerarde, an exchange interne at the University of Iowa Hospitals, Iowa City, received his B.S. and M.S. in Chemistry degrees from Beloit College, and completed his medical course at the University of Wisconsin Medical School in 1948. He has held teaching assistantships in both institutions. During 1949-1950 Dr. Gerarde will study the histochemistry of certain liver diseases, under the direction of Drs. Mattill and Womack of the Departments of Biochemistry and Surgery, The State University of Iowa.

JOHN COLEMAN LAIDLAW, M.A., M.D., of Toronto, Canada. A former medical officer of the Royal Canadian Navy, Dr. Laidlaw attended the University of Toronto, where he obtained the B.A. degree in 1941, the M.D. in 1944, and the M.A., in biochemistry, in 1947. He has served as interne in the Toronto General Hospital and as demonstrator in biochemistry in the University of Toronto. Now an assistant lecturer in biochemistry in the University College, London, England, Dr. Laidlaw pro-

poses to continue studies there under Professor F. G. Young on the metabolism of certain cholinesterase inhibitors in regard to myasthenia gravis. Dr. Laidlaw has been designated by the Board of Regents as the ALFRED STENGEL RESEARCH FELLOW for 1949-1950.

JAMES METCALFE, JR., M.D., of Pigeon Cove, Mass. Presently a Lieutenant in the U. S. Navy, assigned to the Naval Hospital at Newport, R. I., Dr. Metcalfe is a graduate of Brown University (1943), and of the Harvard Medical School (1946). Before entering the Navy, he served as a medical house officer in the Peter Bent Brigham Hospital, Boston, 1946-1947. Dr. Metcalfe will devote his fellowship year to an investigation of the dynamics of circulation, with Dr. Eugene M. Landis, F.A.C.P., in the Department of Physiology, Harvard Medical School.

SAMUEL MOORE PEACOCK, JR., M.D., Philadelphia, Pa. Dr. Peacock is a Bachelor of Arts, Princeton University, 1944, and Doctor of Medicine, University of Pennsylvania School of Medicine, 1948. He is now an interne in the Bryn Mawr Hospital, Bryn Mawr, Pa. As a medical student, Dr. Peacock served as research assistant in the Eldridge R. Johnson Foundation for Medical Physics and the Department of Physical Medicine of the University of Pennsylvania. His fellowship will enable him to return to those departments to conduct cytochemical studies of nervous tissues during growth and other physiological activity, under the direction of Drs. Robert Hodes and Steven M. Horvath.

JACK LEONARD STROMINGER, M.D., Flushing, N. Y. An interne at the Barnes Hospital, St. Louis, Dr. Strominger received his A.B. degree from Harvard University in 1944, and his M.D. from the Yale University School of Medicine in 1948. It is his plan to devote his fellowship to studies of the microchemistry of brain tissue, with Professor O. H. Lowry in the Department of Pharmacology of the Washington University School of Medicine.

EDGAR WOODY, JR., M.D., Nashville, Tenn. Dr. Woody graduated from the University of Georgia in 1941 and took his M.D. degree from the Johns Hopkins University School of Medicine in 1944. Following an internship in the Union Memorial Hospital, Baltimore, Dr. Woody had military service from 1945 to 1947, and then was appointed to internships in pathology and in medicine in the Vanderbilt University Hospital. He will continue studies, now under way in the Departments of Medicine and Pathology of Vanderbilt University School of Medicine, on the combined effect of potassium iodide and streptomycin in tuberculosis.

### *Change in Subscription Rate*

#### ANNALS OF INTERNAL MEDICINE

The subscription rate of \$7.00, domestic, and \$8.00, foreign, for the ANNALS OF INTERNAL MEDICINE has remained unchanged from the inception of the Journal in 1926 to the end of 1948. The cost of producing this Journal has increased 118% since 1940 and the number of pages has been increased over 13% since 1943. The Board of Regents, at their meeting on November 7, 1948, voted to increase the rate of subscriptions from \$7.00 to \$10.00, domestic, and from \$8.00 to \$11.00, foreign, as of January 1, 1949. Members who pay dues will continue to receive the Journal as a part of their membership without further charge.

The increase in the subscription rate is moderate in comparison with the increased cost of publication. The great majority of medical journals have long since increased their subscription rates, in many instances by a much larger percentage than that now being put into effect by the College.

*The American College of Physicians' Directory*

The last complete Directory of the American College of Physicians, containing biographical data of all members, was published during 1941. Due to labor and paper shortages during and immediately after the War, Membership Rosters only have been published, the last edition being for 1948.

The Board of Regents has now authorized the complete revision and republication of the Directory during 1949. The cost will have increased over 1941 by nearly 300%. The prepublication price of the Directory to members of the College will be \$4.00; the price to non-members, institutions and others, \$5.00. In due course, Directory questionnaires, with prepublication order forms, will be distributed to all members of the College.

*New Life Members*

Grateful acknowledgment is made of recent subscriptions to Life Membership by the following Fellows of the American College of Physicians:

Walter M. Solomon, Cleveland, Ohio  
John W. Wilce, Columbus, Ohio  
J. C. Zillhardt, M.D., Binghamton, N. Y.

Charles S. Bluemel, M.D., F.A.C.P., Denver, Colo., has generously given to the College Library of Publications by Members a copy of his new book, "War, Politics, and Insanity," published by The World Press, Inc., 1817 California St., Denver 2, Colo., 1948.

*Associates Should Attend A.C.P. Annual Session*

Attendance at one or more Annual Sessions by Associates before proposal for advancement to Fellowship is prescribed by regulations of the Board of Regents of the American College of Physicians. This regulation was temporarily discontinued during World War II, from 1942 to 1946, because it became obviously impossible for Associates in the armed services to attend and because the Annual Sessions of the College had to be abandoned during part of that time. The regulation is now again in full effect. It is maintained that an Associate must display an abiding interest in the College and in internal medicine or its allied branches. There is no better way in which such an interest can be displayed than by attendance at the Annual Sessions of the College, accepted as the most important postgraduate week in the field on this Continent.

*Proposal of Candidates*

The By-Laws of the American College of Physicians require that proposals of candidates for election to Associateship or Fellowship be filed at least 60 days in advance of action by the Credentials Committee. The next meetings of the Committee are scheduled for February 26 and 27, 1949, and March 26, 1949.

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*VIRGINIA HELD A.C.P. REGIONAL MEETING, AT RICHMOND, OCTOBER 19*

The Virginia Regional Meeting of the American College of Physicians was held at the John Marshall Hotel, Richmond, on October 19, during the meeting of the Medical Society of Virginia. Dr. Staige Blackford, F.A.C.P., Charlottesville, presided as Chairman of the section.

Dr. Charles M. Caravati, F.A.C.P., Richmond, reported to the group on the proceedings of the Board of Governors and the Board of Regents at the San Francisco Annual Session, which he had attended as the alternate Governor for Virginia. Dr.

William B. Porter, F.A.C.P., a representative of the American College of Physicians on the American Board of Internal Medicine, spoke at some length concerning the problems of the Board, its examinations, etc. Dr. J. Morrison Hutcheson, F.A.C.P., Richmond, a former Regent and a former Officer of the College, discussed the qualifications, standards and obligations of members of the College in relation to their communities and in relation to maintaining the highest type of standards in the practice of internal medicine.

Dr. A. Brownley Hodges, F.A.C.P., Norfolk, was unanimously elected Chairman for the coming year, and Dr. James F. Waddill, F.A.C.P., was elected Secretary-Treasurer. The group voted to hold the scientific meeting of the Virginia section at Norfolk sometime early in 1949.

#### NEW JERSEY REGIONAL MEETING NEWARK, NOVEMBER 5, 1948

A large and enthusiastic gathering of members of the College and their guests attended the second annual A.C.P. regional meeting for New Jersey, held under the Governorship of George H. Lathrope, M.D., F.A.C.P., at the Academy of Medicine of Northern New Jersey and the Downtown Club, in Newark. Jerome G. Kaufman, M.D., F.A.C.P., Newark, was chairman of arrangements, and John E. Leach, M.D., F.A.C.P., Paterson, chairman of program. President Walter W. Palmer, New York, and Dr. Alex. M. Burgess, A.C.P. Regent and member of the American Board of Internal Medicine, were guest speakers after dinner. Lemuel C. McGee, M.D., F.A.C.P., Wilmington, Governor for Delaware, and Asa L. Lincoln, M.D., F.A.C.P., New York City, Governor for Eastern New York, presided over the afternoon scientific sessions.

The following scientific program was presented: Diagnosis and Treatment of Hepatic Cirrhosis, Andrew J. V. Klein, M.D., F.A.C.P., Newark, N. J. Ulcerative Colitis: When Should the Internist Advise Surgical Intervention? Manfred Kraemer, M.D., F.A.C.P., Newark, N. J. Insulin Sensitivity, Nathan Swern, M.D., F.A.C.P., Trenton, N. J. Electrocardiographic Booby-Traps, Levi M. Walker, M.D. (Associate), Atlantic City, N. J. Hodgkin's Disease, Its Relation to Other Neoplasms of Lymphoid Tissue, William G. Bernhard, M.D., F.A.C.P., Newark, N. J. The Role of Allergy in Internal Medicine, Robert A. Cooke, M.D., F.A.C.P., New York, N. Y.

#### CONFERENCE COMMITTEE ON GRADUATE TRAINING IN MEDICINE

This Conference Committee on Graduate Training in Medicine has been fully reactivated and will participate with the Council on Medical Education and Hospitals in the inspection and approval of hospitals for graduate training, including residencies. The Committee consists of two representatives each from the American College of Physicians, the American Board of Internal Medicine and the Council on Medical Education and Hospitals. Those representatives are as follows:

For the American College of Physicians:

Dr. LeRoy H. Sloan, F.A.C.P., Chicago, Ill.

Dr. Reginald Fitz, F.A.C.P., Boston, Mass.

For the American Board of Internal Medicine:

Dr. Roy W. Scott, F.A.C.P., Cleveland, Ohio

Dr. Walter L. Palmer, F.A.C.P., Chicago, Ill.

For the Council on Medical Education and Hospitals:

Dr. William S. Middleton, F.A.C.P., Madison, Wis.

Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio

Extensive plans are being rapidly consummated for the initiation of a fully adequate plan of inspection of hospitals.

THE NATIONAL FOUNDATION FOR INFANTILE PARALYSIS ANNOUNCES  
POSTGRADUATE FELLOWSHIPS

*Research*

Research fellowships are available in virology, orthopedic surgery, pediatrics, epidemiology, and neurology. These fellowships are intended to emphasize (1) advanced training in the basic sciences as they apply to the particular specialty and to research, and (2) experience in research, which need not be immediately related to poliomyelitis.

Eligibility requirements: Doctor of Medicine (or when appropriate, a degree of Doctor of Philosophy); a minimum of two years of training on the residency level in the specialized field; presentation of an appropriate program of study and investigation; United States citizenship; sound health, as attested by a physical examination.

*Physical Medicine*

Clinical fellowships are available to physicians who wish to prepare for eligibility for certification by the American Board of Physical Medicine.

Eligibility requirements: Graduation from a Class A school of medicine; completion of a rotating internship of not less than one year in a hospital approved by the Council on Medical Education and Hospitals of the American Medical Association; license to practice medicine in one or more states; citizenship in the United States; sound health, as attested by a physical examination; age limit: 40.

*Public Health*

Fellowships are available to physicians for one year of postgraduate study leading to a Master of Public Health degree at a school of public health approved by the American Public Health Association.

Eligibility requirements: Graduation from a Class A school of medicine; completion of an internship of not less than one year in a hospital approved by the Council on Medical Education and Hospitals of the American Medical Association; license to practice medicine in one or more states; citizenship in the United States; sound health, as attested by a physical examination.

Application may be made to the National Foundation for Infantile Paralysis, 120 Broadway, New York 5, New York, at any time during the year. Selection of candidates will be made on a competitive basis by committees composed of specialists in each field. Awards are based on the individual need of each applicant.

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UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL'S PROGRAM OF POSTGRADUATE  
INSTRUCTION, 1949

The following courses are offered: Psychiatry for General Practitioners (January 31 through February 4); Cardiology (January 31 through February 4); Gastroenterology (February 7 through 11); Endocrinology, Including Diabetes (June 20 through 24); Symposium on Tumors (June 27 through 29); Obstetrics and Gynecology (July 5 through 8); Otorhinolaryngology (September 5 through 9); Ophthalmology (September 12 through 16); Continuation Course in General Medicine (September 19 through December 5); Diseases of the Chest (December 5 through 9).

For detailed information write: Dr. Stacy R. Mettier, Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, California.

RESEARCH GRANTS AND FELLOWSHIPS TO BE MADE AVAILABLE IN 1949 BY THE  
LIFE INSURANCE MEDICAL RESEARCH FUND

Applications for grants in aid of research on cardiovascular problems to begin in 1949 will be received by the Life Insurance Medical Research Fund up to January 15, 1949. Support is available for physiological, biochemical, and pathological research which bears on cardiovascular problems, as well as for clinical investigation in this field. Preference is given to fundamental research. It is expected that about \$500,000 will be awarded for these grants.

Applications for postgraduate fellowships for training in research in 1949-50 will be received by this Fund up to January 1, 1949. Preference is given to candidates who wish to work in the broad field of cardiovascular function or disease and to candidates who wish to work in institutions other than those in which they have obtained most of their experience. A doctor's degree (M.D. or Ph.D.) or the equivalent is required. The annual stipend varies as a rule being between \$2,500 and \$3,500, with larger amounts in special cases. Approximately 12 fellowships will be available.

Later in the year, the Fund will also offer a number of student (pre-doctoral) research fellowships for 1949-50.

Both grants and fellowships will become available on July 1, 1949.

Further information and application blanks may be secured from the Scientific Director, Life Insurance Medical Research Fund, 2 East 103d Street, New York 29, New York.

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COURSE IN ELECTROCARDIOGRAPHIC INTERPRETATION

A course in Electrocardiographic Interpretation for *graduate physicians* will be given at the Michael Reese Hospital Postgraduate School under the personal direction of Dr. Louis N. Katz, Director of Cardiovascular Research. The class will meet each Wednesday from 7:00 p.m. to 9:00 p.m. for a period of 12 weeks, beginning February 9, 1949.

Further information and a copy of the lecture schedule may be obtained on application to Dr. Samuel Soskin, Dean, Michael Reese Hospital Postgraduate School, 29th Street and Ellis Avenue, Chicago 16, Illinois.

## 30TH ANNUAL SESSION

## THE AMERICAN COLLEGE OF PHYSICIANS

WALDORF-ASTORIA HOTEL

NEW YORK, N. Y.

*March 28-April 1, 1949*

The program of General Sessions and Morning Lectures is in charge of the President, Dr. Walter W. Palmer, Public Health Research Institute, Foot of East 15th Street, New York, 9, N. Y. All places are at this time filled, and the program will be published in the February, 1949, Issue of this journal. Many new names and new topics of timely interest have been chosen. The Convocation for the induction of new Fellows and Masters, and the presentation of the John Phillips Memorial Award, the James D. Bruce Memorial Award and the Alfred Stengel Memorial Award, and the announcement of the Research Fellowships, will be held on Wednesday evening, March 30. A distinguished man of national repute will deliver the convocation Lecture.

The program of Hospital Clinics, Panel Discussions, Clinico-Pathological Conferences and entertainment (except for ladies' entertainment) is in charge of the General Chairman, Dr. Franklin M. Hanger, 620 W. 168th Street, New York 32, N. Y. Hospital Clinics will be held on Tuesday and Thursday mornings; many will be conducted in reasonably near-by hospitals and some will be conducted at the Waldorf-Astoria Hotel, some of the distant hospitals, such as in Brooklyn and the Veterans Administration, having arranged to present their clinics at the hotel, and thus save attendants from traveling longer distances. Even the clinics conducted at the hotel will be of highly practical nature with the showing of patients. Panel Discussions covering a wide field of timely topics will be held daily at the hotel, Tuesday through Friday, from 12:00 m. to 1:15 p.m. The Annual Banquet will be held in the Grand Ballroom of the Waldorf-Astoria Hotel on Thursday evening, March 31. An eminently qualified speaker has been engaged. A highly appropriate program of entertainment is being arranged for all, with many unique features for the ladies under the Chairmanship of Mrs. Edgar Stillman. Time is being set aside for theater parties, visits to Radio City, the United Nations, etc.

*Hotel Accommodations.* The Waldorf-Astoria Hotel, Park Avenue and 50th Street, will be official headquarters where registration and meetings will be held. The Belmont-Plaza Hotel, Lexington Avenue and 49th Street, will be supplementary headquarters for housing of speakers and participants in the program. Officers, Regents, Governors and Committeemen of the College and Speakers on the Program should apply for accommodations directly to Mr. E. R. Loveland, Executive Secretary of the College, and not to the Housing Bureau or to hotels direct. Hotel Lexington, Lexington Avenue and 48 Street, has been assigned to the Exhibitors, who should make application for their hotel accommodations through the Medical Exhibitors Association, 616 Stock Exchange Building, Philadelphia 2, Pa.

A fully adequate number of first-class guest rooms has been reserved at near-by hotels within a ten-minute walk of the Waldorf-Astoria Hotel. The Housing Bureau, working through the Committee on Hotels and Transportation, has been set up at 500 Park Avenue, New York 22, N. Y. Applications for rooms should be made to this Bureau, which will make every effort to assign accommodations in keeping with the applicant's wishes. It is necessary that five choices of hotels be indicated, and that a reasonable range of rates desired be shown. Whenever possible, arrangements should be made for occupancy of rooms accommodating two persons. Hotels will

confirm each reservation after its receipt from the Housing Bureau. All applicants are urgently requested to notify the Housing Bureau promptly if they find it impossible to attend, thus releasing their accommodations to other physicians.

*List of Hotels*

<i>Hotel</i>	<i>Type of Room and Rate*</i>
Waldorf-Astoria Park Avenue and 50th Street	100 doubles—\$10.00 to \$16.00 25 suites—18.00 to 32.00
Belmont-Plaza Lexington Avenue and 49th Street	90 doubles—\$6.50 to \$9.50 5 suites—12.00 to 15.00
Abbey 149 W. 51st Street	12 singles—\$3.75 to \$5.00 38 doubles—6.00 to 8.00
Ambassador Park Avenue and 51st Street	10 doubles—\$9.00 to \$14.00 5 suites—16.00 to 25.00
Barclay 111 E. 48th Street	50 doubles—\$11.00 to \$13.00
Biltmore Madison Avenue and 43d Street	100 doubles—\$10.00 to \$17.00
Commodore Lexington Avenue and 42nd Street	70 singles or doubles: singles—\$5.50 to \$7.50 doubles—8.50 to 10.00 200 twins—11.50 15 combinations—\$13.00
Delmonico 502 Park Avenue	6 singles—\$10.00 10 suites—18.00 to 22.00
Gotham Fifth Avenue and 55th Street	10 doubles—\$9.00 to \$14.00
New Weston 34 E. 50th Street	30 doubles—\$8.00 to \$10.00 5 suites—12.00 to 20.00
Park Central Seventh Avenue and 56th Street	50 doubles—\$8.50 to \$10.00 75 suites—10.00 to 14.00
Piccadilly 227 W. 45th Street	75 doubles—\$6.00 to \$8.00
Plaza Fifth Avenue and 59th Street	10 singles—\$9.00 to \$12.00 40 doubles—10.00 to 18.00
Roosevelt Madison Avenue and 45th Street	50 singles—\$6.50 to \$10.00 350 doubles—10.50 to 15.00
St. Regis Fifth Avenue and 55th St.	3 singles—\$8.00 to \$10.00 6 doubles—12.00 to 14.75
Shelton Lexington Avenue and 49th Street	25 singles—\$4.50 to \$6.50 75 doubles—6.50 to 8.00

\* Subject to 5% New York City Sales Tax.

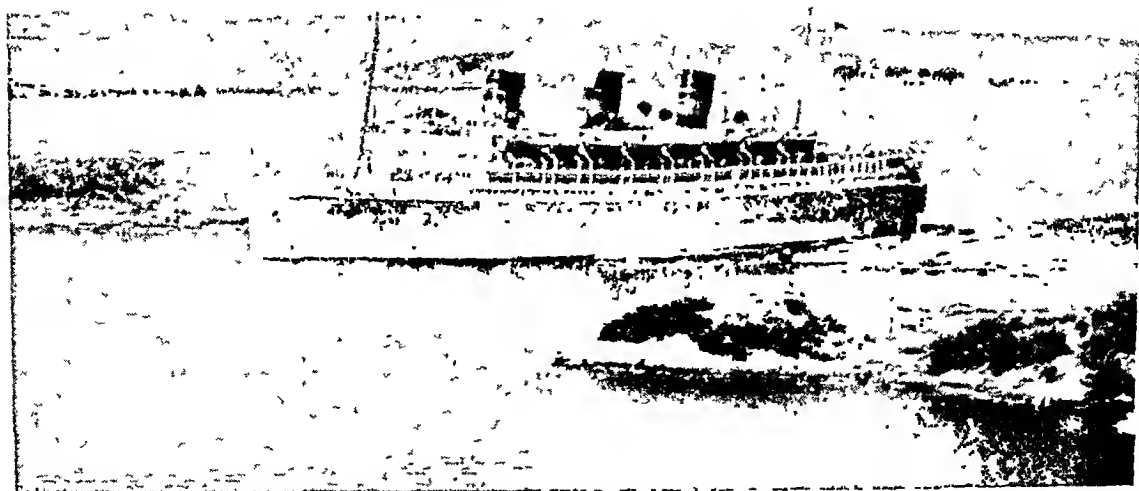


Sheraton 303 Lexington Avenue	10 doubles—\$8.00 to \$10.00 10 suites—10.00 to 12.50
Taft Seventh Avenue and 50th Street	50 singles—\$4.00 to \$7.00 150 doubles—6.50 to 9.00
Vanderbilt (10 minutes by cab) Park Avenue and 34th Street	10 singles—\$4.50 to \$7.00 15 doubles—8.00 to 10.00
Victoria Seventh Avenue and 51st Street	10 singles—\$5.00 65 doubles—7.00 to 9.00
Warwick 65 W. 54th Street	75 doubles—\$12.00 25 suites—20.00
Wentworth 59 W. 46th Street	20 doubles—\$7.00 to \$8.00 15 suites—12.00 to 14.00
Winthrop Lexington Avenue and 47th Street	6 doubles—\$7.00 to \$9.00

<sup>4</sup> Subject to 5% New York City Sales Tax.

#### POST-CONVENTION CRUISE

Following 30th Annual Session A.C.P., New York City



*The Queen of Bermuda at Two Rock Channel en route to Hamilton Harbor.*

The Convention Tour to and from the San Francisco Annual Session of the College during the spring of 1948 met with such acclaim among those who took ad-

vantage of it that numerous requests have come in for some other post-convention event in 1949, which led to the decision to conduct a Post-Convention Cruise to Bermuda following the 30th Annual Session in New York City from March 28 through April 1, 1949. The cruise has been arranged to leave New York City at 12 o'clock noon, Monday, April 4, using the steamship, *Queen of Bermuda*, with the following schedule:

- April 4—Leave New York 12:00 noon; Upper and Lower Bays, the famous skyline, tea, dancing.
- April 5—The Gulf Stream, a lazy day at sea. Movies, Tea, Concert, Dancing.
- April 6—Bermuda. Arrive Five Fathom Hole at 7:00 a.m. and cruise along the colorful North Shore into Great Sound and Hamilton Harbor, one of the loveliest in the world. Go ashore at 9:00 a.m. Hotel Bermudiana.
- April 7—Motor or carriage drives to St. George's, Somerset, Gibb's Hill, or Spanish Point; time to visit the celebrated caves and coral underseas gardens; to shop; to golf; to follow the camera or other diversions.
- April 8—Leave Hamilton, 3:00 p.m. via the Great Sound and North Shore.
- April 9—Again in the Gulf Stream; a variety of entertainment.
- April 10—Monday; arrive New York, 9:00 a.m.

Bermuda is a delightful vacation center with landscapes and marine views enchanting in their loveliness.



A quiet cove in Hamilton Harbor.

The *Queen of Bermuda* is one of the handsomest and most luxuriously equipped ships coming into New York.

A special, illustrated booklet is being prepared. For full information, plan of the ship, booklet on Bermuda, and answers to your questions, write to Mr. Leon V. Arnold,

Travel Consultant, 36 Washington Square West, New York, 11, N. Y. Mr. Arnold handled the Bermuda arrangements for the American College of Physicians in 1938 and will be the official conductor in 1949.

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### A.C.P. POSTGRADUATE COURSES

#### Spring, 1949, Schedule

The following schedule of courses has been approved by the Advisory Committee on Postgraduate Courses and the Board of Regents for the spring of 1949. The Preliminary Postgraduate Bulletin will be published during December and distributed to all members of the College and to those who have requested the entry of their names on the non-member mailing list. A registration form will accompany the Postgraduate Bulletin.

**MEDICAL ASPECTS OF NUCLEAR ENERGY**—Bureau of Medicine and Surgery, U. S. Navy, Medical Department of the U. S. Army, the Armed Forces Special Weapons Project, the Atomic Energy Commission, the Air Force, the U. S. Public Health Service, and the Veterans Administration, Washington, D. C.; Lt. Col. Karl Houghton, (MC), USA, Chairman; eight days, January 24–February 1, 1949; Fee: \$40.00, A.C.P. Members; \$80.00, Non-members; free to medical officers from the participating agencies.

The class will meet at the Sternberg Auditorium, Army Medical Center, Washington, D. C., where excellent facilities are available, such as the new radiation laboratory for demonstrations and instrument problems. One of the big problems in this field is the education of both service and civilian physicians. Never before have all agencies combined to make available, through the American College of Physicians, a course of such importance and significance. The medical profession has a moral responsibility to learn all that is available on this subject. An effort will be made to include the nature of ionizing radiation as it relates to atomic fission, the methods of detection and evaluation of the hazard, the biological effects of radiation, the possibilities of protection and avoidance, and present concepts of treatment. Two days may be added to the course to cover the Medical Effects of Atomic Explosion. Specific information on isotopes and laboratory procedures has been added to the course.

Registration for this course is immediately available on application for registration forms.

**GASTRO-ENTEROLOGY**—University of California Medical School and Stanford University School of Medicine, San Francisco, Calif.; T. L. Althausen, M.D., F.A.C.P., and Dwight L. Wilbur, M.D., F.A.C.P., Directors; one week, February 7–12, 1949; Fee: \$30.00, A.C.P. Members; \$60.00, Non-members.

The detailed outline of this course has been published and is available. Registration should be consummated without delay. It is anticipated there will be facilities for several non-members.

**THE HEMATOLOGIC EMPHASIS IN CLINICAL MEDICINE**—Ohio State University College of Medicine, Columbus, Ohio; Charles A. Doan, M.D., F.A.C.P., Director; one week, February 14–19, 1949; Fee: \$30.00, A.C.P. Members; \$60.00, Non-members.

This is a repetition of a course that has been most successfully given on previous occasions. It is one of exceptional merit.

**INTERNAL MEDICINE**—Massachusetts General Hospital, Boston, Mass.; James H. Means, M.D., F.A.C.P., Director; two weeks, March 7–19, 1949; Fee: \$60.00, A.C.P. Members; \$120.00, Non-members.

It has been several years since Dr. Means directed a course for the College, and special gratification is felt by the members for the opportunity to take this exceedingly fine course again.

**ELECTROCARDIOGRAPHY**—Massachusetts General Hospital, Boston, Mass.; Conger Williams, M.D., Director; one week, April 25-30, 1949; Fee \$60.00, A.C.P. Members; \$120.00, Non-members.

This course was first given during May, 1948. The class was oversubscribed, and early registration is recommended to members of the College. It would appear improbable that many non-members can be accommodated. The course is designed to acquaint the student with the modern theory of electrocardiography and its clinical application.

**CARDIOLOGY**—Philadelphia Institutions; William G. Leaman, Jr., M.D., F.A.C.P., Director; one week, May 2-7, 1949; Fee: \$30.00, A.C.P. Members; \$60.00, Non-members.

The class will meet at the Philadelphia General Hospital. The faculty for this course will include leading teachers in cardiology from various medical schools of Philadelphia and other institutions of the East. Early registration is recommended because it is anticipated that the demand may exceed the facilities.

**PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE**—University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Julius H. Comroe, Jr., M.D., F.A.C.P., Director; one week, May 9-14, 1949; Fee: \$30.00, A.C.P. Members; \$60.00, Non-members.

This course was first given during 1947 by Dr. Comroe and was one of the most popular courses ever organized under the College. It is planned for internists who are interested in learning why symptoms occur, how drugs act, and why and how clinical physiological tests are used in diagnosis. The faculty will consist of many authorities from Philadelphia institutions and also from other cities, such as Boston, New York, Baltimore, Chicago, Cleveland, and elsewhere.

**ALLERGY**—University of Pittsburgh School of Medicine, Pittsburgh, Pa.; Leo H. Crip, M.D., Director; one week—May 16-21, 1949; Fee: \$30.00, A.C.P. Members; \$60.00, Non-members.

At the time this announcement is sent to press, this course is yet in a tentative state. The course, however, has been approved by the College and awaits assignment of a date and other details. A close, coöperative plan with the University of Pittsburgh, the American Academy of Allergy, and the American College of Physicians will be established, and the course should be extremely valuable to the internist who wishes instruction in allergy, as well as to the allergist who desires to be kept up-to-date.

**ENDOCRINOLOGY**—Tufts College Medical School, Boston, Mass.; Edwin B. Astwood, M.D., F.A.C.P., Director; one week, June 13-18, 1949; Fee: \$30.00, A.C.P. Members; \$60.00, Non-members.

This is a new course on the College schedule. All of the details have been concluded, and it is confidently expected that this course will be one of the outstanding courses on the College program.

Preliminary Outline A.C.P. Postgraduate Course  
**MEDICAL ASPECTS OF NUCLEAR ENERGY**  
 Washington, D. C., Jan. 24–Feb. 1, 1949

	Mon., Jan. 24	Tues., Jan. 25	Wed., Jan. 26	Thurs., Jan. 27	Fri., Jan. 28	Mon., Jan. 31	Tues., Feb. 1
A.M. 9:00 – 10:00	Introduction and Scope of Course	Informal Dis- cussion of Basic Physics	Radiation De- tection and Measurement	Physical and Laboratory Diagnosis of Radiation Injury	Production of Radioisotopes	Laboratory In- strumentation	Uses of $P^{32}$
10:00 – 11:00	Basic Atomic and Nuclear Physics	Types of Per- sonnel Injuries at Hiroshima and Nagasaki		Therapy of Radiation Injury	Procurement and Safe Han- dling of Radio- active Material	Assay of Radioactive Material	Uses of $P^{32}$
11:00 – 12:00		Biological Effects of Ioniz- ing Radiation		Therapy and Handling of Mechanical and Thermal Injuries	Decontamina- tion Problems	Dosage Calcu- lation	Uses of $Na^{24}$
P.M. 1:00 – 2:00	Radioactivity and Properties of Particles		Fundamentals of Radiation Pathology	Internal Radia- tion Hazard	Diagnostic and Therapeutic Use of Isotopes	Principles of Tracer Tech- niques	Uses of Miscel- laneous Isotopes
2:00 – 3:00	Fission and Bomb Phe- nomena	Radiation Sick- ness		Psychological Implications of Atomic Bomb- ing	International Implications of Nuclear Energy	Principles of Radio- chemistry	Isotope Labora- tory Organiza- tion and Admin- istrative Prob- lems
3:00 – 4:00	Nuclear Energy —British Film Parts I, II, III	Nuclear Energy —British Film Parts IV, V	Medical Effects of Atomic Bombs Japa- nese Film	Nuclear Energy March of Time Film and Opera- tions Crossroads		Radioauto- graphic Tech- niques	Guest Speaker

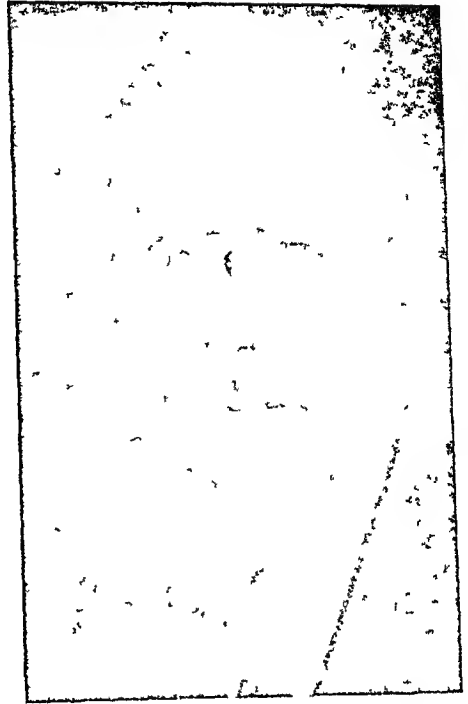
## OBITUARIES

Dr. James Alexander Miller, President of the American College of Physicians in 1935-1936, died at his summer home in Black Point, Conn., July 29, 1948.

Dr. Miller was born in Roselle, N. J., March 24, 1874. He was graduated from Princeton University in 1893 and received his A.M. degree there in 1894. His medical degree was awarded by the College of Physicians and Surgeons, Columbia University, in 1899. Early in his medical career, he spent his summers in association with Dr. Edward Livingston Trudeau at Saranac Lake. Dr. Miller was greatly inspired by this personal and professional association, and its influence lasted throughout his life. Seeing the need of organized social, public health, and medical work against tuberculosis, Dr. Miller soon became identified with organizations in New York City through which he was able to direct his efforts. These included the Charity Organization Society, the New York Tuberculosis and Health Association, and the Tuberculosis Service of Bellevue Hospital. He came in close contact with the numerous aspects of the tuberculosis problem and was early convinced of the necessity of directing the attack from various fronts. In the public health field he helped organize the New York Tuberculosis and Health Association and the National Tuberculosis Association, serving as President of the former from 1920 to 1929, and of the latter in 1921 and 1922. In the social service field he continued active in the Community Service Society which was partly the offspring of the Charity Organization Society. At Bellevue Hospital he interested a group of loyal associates who helped him transform an unspeakably neglected tuberculosis service into one of the most outstanding of its type in the world. At the same time, recognizing the great need for medical education in this branch of medicine, Dr. Miller organized a course of instruction for his resident hospital staff and also for the students of the College of Physicians and Surgeons of Columbia University. In these relationships he served as Visiting Physician in Charge of the Tuberculosis Service, and Professor of Clinical Medicine. Simultaneously, he assumed more and more responsibility for the development of the work at Trudeau Sanatorium, finally serving as President of the Board of Trustees for a number of years.

These activities indicate only in small degree the scope of his interest and resourcefulness, the ample reserve of energy with which he was endowed, and the limitless generosity with which he gave of his time and talents to many worthy projects. He was President of the American Climatological and Clinical Association in 1914 and a member of various other medical societies. From 1945 until the time of his death, he was an alumni trustee of Columbia University.

In the American College of Physicians Dr. Miller's record of contributions is most distinguished, and was recognized by the award of Mastership in 1941. He served as a member or chairman of numerous committees, including the Board of Regents,



DR. JAMES ALEXANDER  
MILLER

the Executive Committee, the Committee on Standards of Admission, the Committee on Public Relations and the Committee on Future Policy for the Development of Internal Medicine. His leadership as President was outstanding, and his energy and farsightedness lent a great impetus to the sound and progressive development of the College. He did much to define its objectives, including educational activities, sound finance, the establishment of a permanent home in Philadelphia and the creation of the American Board of Internal Medicine. He exercised similar leadership in other organizations and became the President of the New York Academy of Medicine from 1937 to 1938. In 1947 the Academy awarded him a medal in recognition of his unique position as "its most distinguished and beloved Fellow and one of the great benefactors of mankind." Numerous other honors came to him, including the Trudeau Medal of the National Tuberculosis Association in 1944, election as a Chevalier of the French Legion of Honor in 1918, following his service in the American Red Cross and as Medical Director of the Rockefeller Commission for the Prevention of Tuberculosis, and honorary degrees from Princeton (Sc.D., 1936), Columbia (Sc.D., 1930) and New York Universities (Dr. P. H., 1937).

The logical succession of Dr. Miller to leadership in so many activities is explained by his administrative capacity, his vision, his ability to penetrate problems, evaluate their merits and formulate practical solutions, and his appreciation of the qualities of men and his ability to inspire them to exercise these qualities for useful purposes. He recognized no limit of progress or improvement in the organizations and projects in which he was interested and could always see a better future, but was sufficiently realistic to know that progress could be achieved only by gradual steps and hard work. He never spared himself in sharing the labor; thus, through his magnanimity, fine spirit and constant hope, he stimulated many others to work with him toward the ideal. With all this, he cared for a busy private practice and became the leader in tuberculosis work in his community. He had an ample following of loyal and admiring patients. There are few physicians who have ever won the gratitude of a community like that which came to Dr. Miller, and few who have exemplified the best qualities of a physician in so many ways.

J. BURNS AMBERSON, M.D., F.A.C.P.

### DR. JEREMIAH FLETCHER LUTZ

Jeremiah Fletcher Lutz, M.D., F.A.C.P., of Glen Rock and York, Pa., died in the Veterans Administration Hospital, Fort Howard, Md., of generalized atherosclerosis on September 11, 1948, and was buried in Glen Rock with Masonic rites. Dr. Lutz had retired from active practice about four months previously because of failing health.

Born in Baltimore on November 25, 1872, Dr. Lutz attended the Baltimore Polytechnic Institute, Sadler's Bryant and Stratton Business College, and received his medical degree in 1894 from the College of Physicians and Surgeons of Baltimore, now amalgamated with the University of Maryland School of Medicine. He interned at the Bay View Hospital (now the Baltimore City Hospital, 1894-96, and pursued postgraduate work at the New York Polyclinic Hospital, Presbyterian Eye, Ear, Nose and Throat Hospital, the Baltimore School of Roentgenology, and the Johns Hopkins University School of Medicine (under Dr. F. H. Baetjer). He took numerous other shorter courses in radiology. Licensed to practice in Maryland and Pennsylvania, Dr. Lutz limited his work to radiology in 1917, and subsequently became a diplomate of the American Board of Radiology.

During World War I, Dr. Lutz served as chief of the X-ray Department in the Army General Hospital No. 2, at Fort McHenry, Md., with rank of Major. He was roentgenologist, 1920-26, to the Kernan Hospital for Crippled Children, Baltimore; also, 1921-24, to the Sinai Hospital, and, 1921-26, to the Baltimore Eye and Ear

Hospital. He served the York Hospital, York, Pa., in a similar capacity from 1930 until his retirement in 1948. During the recent War, Dr. Lutz was associate roentgenologist to Medical Advisory Board No. 4, and examining physician to Local Board No. 1, Pennsylvania Selective Service. He was a member of the Pennsylvania State Medical Society, Philadelphia Roentgen Ray Society, and the Society for the Study of Neoplastic Diseases; a past president of the York County Medical Society and the York County Medical Club; a Fellow of the American Medical Association, the Radiological Society of North America, the American College of Radiology, and, since 1939, the American College of Physicians. Prominent in Masonic circles, Dr. Lutz was affiliated with numerous organizations and delivered many illustrated lectures on the "History of Masonry," the product of years of painstaking research. He was also the author of a number of published papers on radiology.

To a rare degree, Dr. Lutz combined thorough generalized clinical and specialized training, fine judgment and genuine human sympathy. Over a long period of years, he had given unselfishly of his services to every phase of organized medicine, and he will be deeply mourned by a large host of friends, both in and out of the profession, as well as by the members of his most devoted family.

JULIUS H. COMROE, SR., M.D., F.A.C.P.

#### MR. WILL C. BRAUN

Probably never before have these columns contained the obituary of a layman. Mr. Will C. Braun, Business Manager Emeritus of the American Medical Association, stands in a category all his own. He was born August 24, 1868, and died September 12, 1948, at the age of 80 years. He had devoted 56 of those 80 years to the work of the American Medical Association and was the most widely known layman associated with the medical profession. He had a large hand in the history and growth of his organization, dating back to its early beginnings and carrying through to the great organization it is today. He served actively until 1946 as the Business Manager and then was retired, being succeeded by Mr. Thomas R. Gardiner.

Mr. Braun will be affectionately remembered by a great host of physicians, by advertisers, exhibitors, and the numerous organizations that had frequent contact with him over so many years.

E. R. LOVELAND

#### DR. EDWARD WINFIELD MISKALL

Dr. Edward Winfield Miskall died suddenly of coronary occlusion, on his forty-eighth birthday on August 13, 1948, in the midst of an active cardiologic practice in East Liverpool, Ohio. He was born and reared in East Liverpool, and received his Bachelor of Science degree in 1924, and his medical degree in 1926 from the Ohio State University. He served his internship at Mercy Hospital, Springfield, Mass. Following a period of general practice, he went to the Massachusetts General Hospital, where, for two years, he indulged his interest and perfected his training in the special field of his choice under Dr. Paul White. Returning to East Liverpool in June 1934, he became an outstanding consultant in Cardiology, attracting patients from many communities in the Tri-State District. He was elected to fellowship in the American College of Physicians in 1936, and became a diplomate of the American Board of Internal Medicine in 1945. He was a member of the medical staff and director of the Clinical Laboratories of the East Liverpool City Hospital. He served as City Health Commissioner for five years until the increasing demands upon his direct professional services prevented his continuing this activity. He was consulting cardio-



logist to the Salem City Hospital and was past president of the Columbiana County Medical Society.

Dr. Miskall continued throughout his relatively brief medical career to be a student of disease and made each patient the object of special and thorough study. The passing of Dr. Miskall has left a great void in his community. Both fellow physicians and patients had the highest respect for his professional ability.

CHARLES A. DOAN, M.D., F.A.C.P.,  
Governor for Ohio

### DR. ANDREW BAPTISTE RIVERS

Dr. Andrew B. Rivers was born December 10, 1894, at Rollingstone, Minn. He attended St. Francis College, St. Francis, Wis., from 1906 to 1913; received the degree of M.D. in 1917 from Creighton University and was an intern at the City and County Hospital, St. Paul, Minn., from July, 1917, to October, 1918. He served as lieutenant in the Medical Corps of the United States Navy during World War I. He was assistant in medicine at the University of Minnesota from May to November, 1919, and entered the Mayo Foundation as a fellow in medicine on January 15, 1920; received the degree of M.S. in Medicine in 1929 from the University of Minnesota and of M.A. in 1930 from St. Francis College. At the time of his death he was consultant in medicine, the Mayo Clinic, and associate professor of medicine, the Mayo Foundation, Graduate School, University of Minnesota.

Dr. Rivers was a fellow of the American College of Physicians and the American Medical Association, and a member of the American Gastro-Enterological Association, the Central Clinical Research Club, the Central Society for Clinical Research, Sigma Xi and Phi Beta Pi.

Dr. Rivers had published about ninety articles, chiefly in the field of gastroenterology, and at the time of his death was preparing a monograph on peptic ulcer. Dr. Rivers was a skilled internist with a great capacity for friendship. He was admired and respected by patients, students and associates. He died from acute coronary thrombosis on October 3, 1948.

E. V. ALLEN, M.D., F.A.C.P.,  
Governor for Minnesota

### DR. C. FREDERIC ROCHE

The name of Dr. C. Frederic Roche, beloved pioneer physician of Miami Beach Fla., is written indelibly into the record of growth of his chosen community. He established his practice there when Miami Beach was a struggling young resort, and at his death he was one of the outstanding physicians in the practice of internal medicine in the Miami area. Much of his time, effort and enthusiasm had been spent in the building of what is now a thriving city.

Dr. Roche was born in Bay City, Mich., in 1888. He was graduated in medicine from the University of Michigan in 1919 and began his practice in Florida shortly thereafter. He organized the Miami Beach Department of Health and served as its director for many years. He served as chief of the Cardiac Clinic and medical service of St. Francis Hospital and as staff member of Victoria Hospital, and was a past president of the Miami Heart Association. He became a Fellow of the American College of Physicians in 1930.

Throughout his career he was esteemed for his progressive attitude, his diligent efforts to better the health resources of his community, his kindness and devotion to his friends. He gave unsparingly and unselfishly of his strength and died at the peak of his career on January 17, 1948.

WILLIAM C. BLAKE, M.D., F.A.C.P.,  
Governor for Florida

## DR. THOMAS TROVILLO SHEPPARD

Thomas Trovillo Sheppard, M.D., of Pittsburgh, died July 5, 1948, at the age of 56.

A graduate of Yale University and, in medicine, of the Columbia University College of Physicians and Surgeons, Dr. Sheppard was for many years on the medical staff of the St. Francis, Western Pennsylvania, and Elizabeth Steele Magee Hospitals. He was assistant professor of medicine in the University of Pittsburgh and director of the Renziehausen Foundation for Diabetic Children in the Children's Hospital. A Fellow of the American Medical Association, Dr. Sheppard was a member of the Pittsburgh Academy of Medicine, Clinical Pathological Society of Pittsburgh, Pittsburgh Society for Biological Research, Allegheny County and Pennsylvania State Medical Societies and the American Diabetes Association. He became an associate of the American College of Physicians in 1928.

## DR. FRANCIS H. SMITH

Dr. Francis Henney Smith, an outstanding Southern psychiatrist and a Fellow of the American College of Physicians since 1923, died at his home at Abingdon, Va., on July 1, 1948.

Born at Lexington, Va., April 12, 1881, Dr. Smith obtained the A.B. degree from Fredericksburg College and the M.D. degree from the Medical College of Virginia in 1904. He practiced for a time in Lewisburg, W. Va., before going to Abingdon where he served as an internist in the George Ben Johnston Memorial Hospital. Dr. Smith was a former president of the Medical Society of Virginia and a member of the Medical Examining Board of Virginia, as well as the Southwestern Virginia Medical Society, the Southern Medical Association, and the American Medical Association.

## DR. CLARENCE M. TRIPPE

Dr. Clarence Morton Trippe of Asbury Park, a former president of the Charlotte, N. C., and Asbury Park, N. J., Medical Associations, and former vice president of the New Jersey Medical Society, died on August 25, 1948. He held the degrees of Bachelor and Master of Arts from Hamilton College and was a graduate of North Carolina Medical College and the College of Physicians and Surgeons of Columbia University. Following postgraduate studies in neuropsychiatry at the Neurological Institute and the Presbyterian and Roosevelt Hospitals in New York, Dr. Trippe served as Chief of Neurology in the Presbyterian, Mercy, and St. Peter's Hospitals, Charlotte, 1912-1915. During World War I he taught at Columbia University, and subsequently became Attending Neuropsychiatrist in the Veterans Administration Hospital, Lyons, N. J., and a member of the staff of Monmouth Memorial Hospital, Long Branch, N. J. A diplomate of the American Board of Neurology and Psychiatry, Dr. Trippe was a fellow of the American Medical Association and of the American College of Physicians, and a member of the Monmouth County Medical Society.

## DR. CLARENCE KRAUS WEIL

Dr. Clarence Kraus Weil, an Associate of the American College of Physicians, died suddenly from coronary thrombosis in Montgomery, Ala., on May 5, 1948, at the age of 48 years. He was a native of Montgomery where he had continued to reside throughout his life. He received his B.S. degree from the University of Alabama in 1919, his M.D. degree from the Columbia University College of Physicians

and Surgeons in 1923, and did postgraduate work at Mount Sinai Hospital, New York. He was a veteran of World War II, having retired from the Army in 1946 with the rank of Lieutenant Colonel.

At the time of his death Dr. Weil was in active practice in Montgomery, where he was known for his interest in both civic and medical affairs. He had served as chairman of the Board of Censors and as president of the Montgomery County Medical Society; as counsellor for the Alabama State Medical Association; as vice chairman of the Section on Allergy of the Southern Medical Association. He was a diplomate of the American Board of Internal Medicine, a member of the Southeastern Allergy Association and the Chattahoochee Valley Medical Association, and a Fellow of the American Medical Association and the American Academy of Allergy.

Dr. Weil's death at the peak of his influence is regrettable.

E. DICE LINEBERRY, M.D., F.A.C.P.,  
Governor for Alabama

### DR. ANDREW BLAIR

Andrew Blair, M.D., F.A.C.P., a diplomate of the American Board of Internal Medicine, of Charlotte, N. C., died June 3, 1948. He was born at Carlisle, Pa., in 1896. He received his B.S. and A.M. degrees in 1921 and 1925, respectively, from Dickinson College. After graduating from the University of Pennsylvania School of Medicine in 1924, Dr. Blair thereafter served on the medical staffs of Presbyterian, Mercy, St. Peters, and Charlotte Memorial Hospitals in Charlotte, N. C. Dr. Blair was a member of the Medical Society of the State of North Carolina, and the Tri-State Medical Association; a former secretary of the Mecklenburg County Medical Society; a fellow of the American Medical Association and, since 1940, of the American College of Physicians.

### DR. DANIEL DELOS COMSTOCK

Dr. Daniel Comstock was born in Tioga County, Pa., on April 29, 1880, and died in Oakland, Md., July 29, 1948, while vacationing there and recuperating from a previous heart attack. He received his preliminary education in Tioga County and attended business college in Elmira, N. Y. Later he joined staff workers at Battle Creek Sanitarium where he obtained nursing instruction. In 1902 he entered the American Medical Missionary College, from which he received his Doctor of Medicine degree in 1906. One year after graduating from medical school he came to California where he became prominent both in medical practice and education. In 1918 he became senior assisting physician, Los Angeles County Hospital, and in 1920, chief of the medical staff of the White Memorial Hospital and clinical professor of medicine in the College of Medical Evangelists.

Dr. Comstock was a diplomate of the American Board of Internal Medicine. He was a member of the Los Angeles County Medical Society, California and American Medical Associations, and the Los Angeles County Heart Association. He became a Fellow of the American College of Physicians in 1932.

Dr. Comstock was highly respected by the members of the medical profession and will be greatly missed by those who knew him.

LELAND P. HAWKINS, M.D., F.A.C.P.,  
Governor for Southern California

### DR. CHARLES V. CRANE

Charles Vernon Crane, M.D., F.A.C.P., of Grand Rapids, Mich., died October 10, 1948, of coronary thrombosis at the age of 66. He was a graduate of the Uni-

versity of Michigan Medical School in 1904, and had practiced in Grand Rapids for more than 25 years. He was one of Grand Rapids' leading internists and enjoyed the confidence of his patients and colleagues. A conscientious physician, he was interested in medical problems but always concerned about his patients' welfare. He leaves a host of loyal friends and associates.

Following his graduation from medical school, Dr. Crane interned in the U. S. Marine Hospital, Detroit, in 1904-1905. He practiced and held appointments from 1906 to 1916 in Tawas and Bay Cities. Entering the Medical Reserve Corps of the U. S. Army in 1916 as lieutenant, Dr. Crane served until 1919, when he was discharged as a lieutenant colonel. A diplomate of the American Board of Internal Medicine, Dr. Crane held appointments to the medical staffs of the Blodgett Memorial, Butterworth and St. Mary's Hospitals, and was consultant to the Clark Memorial and Isabella Homes.

Dr. Crane was elected to fellowship in the American College of Physicians in 1936. He was also a member or fellow of the Kent County and Michigan State Medical Societies, the American Medical, American Heart and American Diabetes Associations, and the Inter-State Post Graduate Medical Association of North America.

A. J. BAKER, M.D., F.A.C.P.

#### DR. OTHO AUGUST FIEDLER

Dr. Otho A. Fiedler of Sheboygan, Wis., a Fellow of the American College of Physicians since 1929, died June 22, 1948. Born at Stockbridge, Wis., March 9, 1873, Dr. Fiedler attended Marquette University School of Medicine and did postgraduate work at the University of Vienna. From 1902 to 1906, he served as Professor of Chemistry, and from 1912 to 1914, as Professor of Medicine at Marquette. He served in the Army Medical Reserve Corps in World War I and subsequently became Chief of Medical Service of the Sheboygan Clinic and St. Nicholas Hospital as well as Preceptor in the University of Wisconsin Medical School. A diplomate of the American Board of Internal Medicine, Dr. Fiedler was a past president of the Wisconsin State Board of Health, the Sheboygan County Medical Society, and the State Medical Society of Wisconsin; also a fellow of the American Medical Association.

#### DR. JAMES KING HALL

Dr. James King Hall, an organizer of Westbrook Sanatorium, Inc., Richmond, Va., and its president since 1911, died September 10, 1948. Born in North Carolina on September 28, 1875, Dr. Hall received the M.D. degree from Jefferson Medical College of Philadelphia in 1904, and the A.B. and LL.D. degrees from the University of North Carolina in 1901 and 1935, respectively. He was a diplomate of the American Board of Psychiatry and Neurology.

Dr. Hall was an associate editor of Southern Medicine and Surgery and of Diseases of the Nervous System. He was a former president of the American and Southern Psychiatric Associations, Association of Private Psychiatric Hospitals, Tri-State Medical Association of Virginia and the Carolinas, and the Richmond Academy of Medicine; a vice-president of the Medical Society of Virginia; and a member of many other professional organizations. A member of the old American Congress on Internal Medicine, Dr. Hall became an Associate of the American College of Physicians in 1923.



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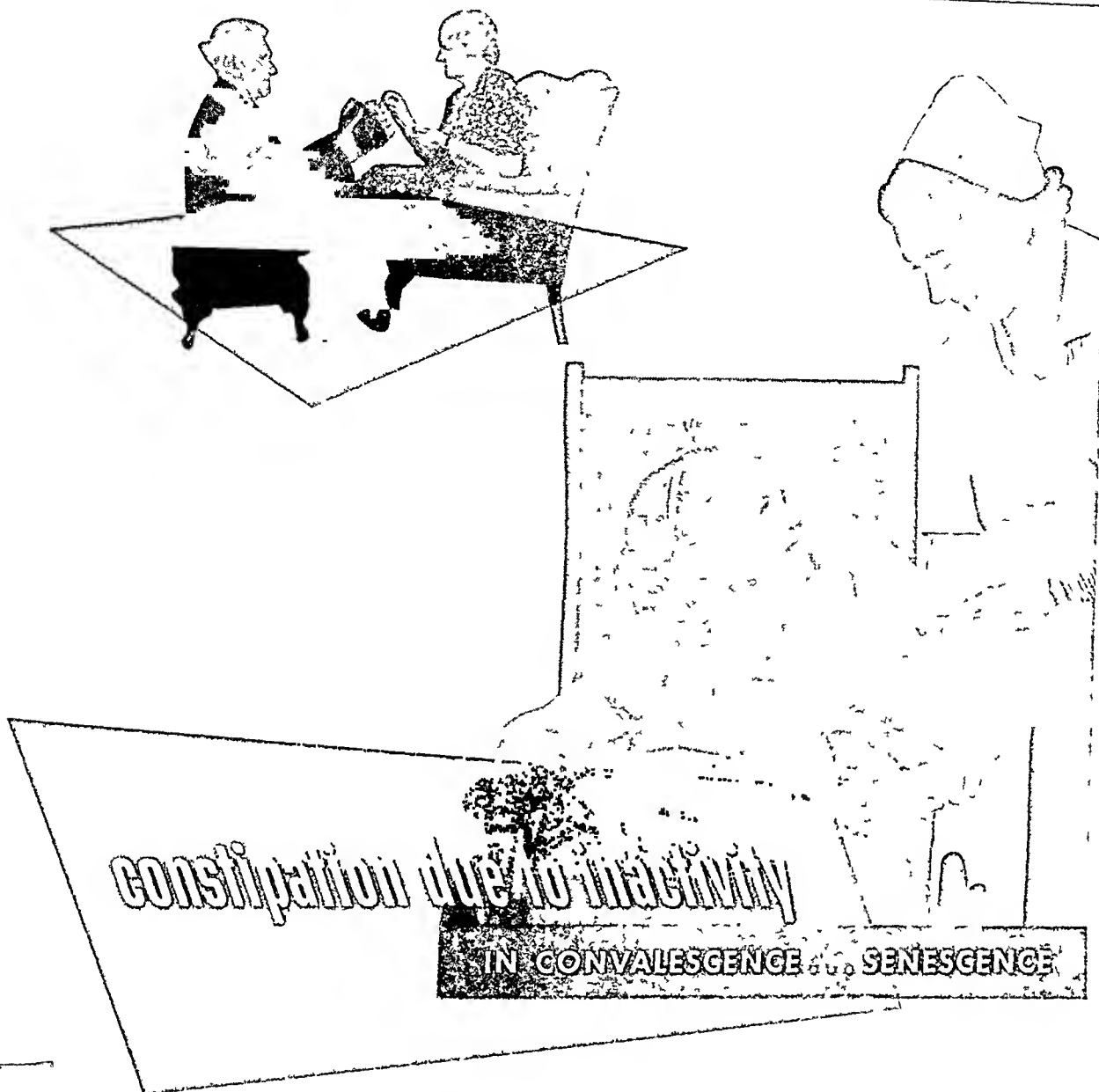
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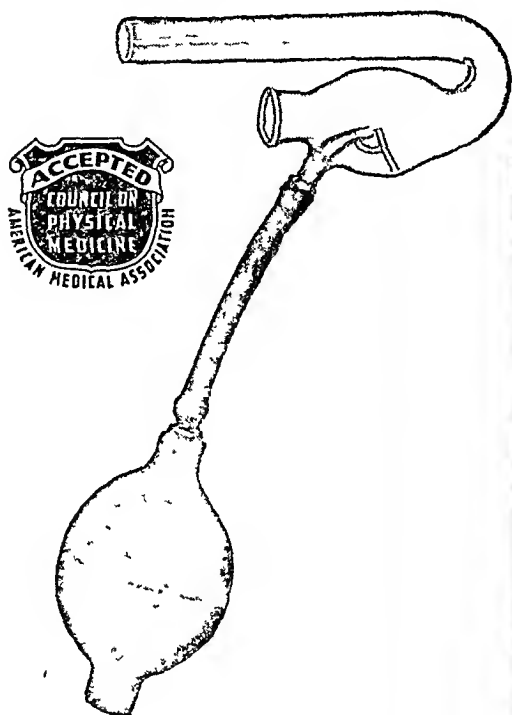


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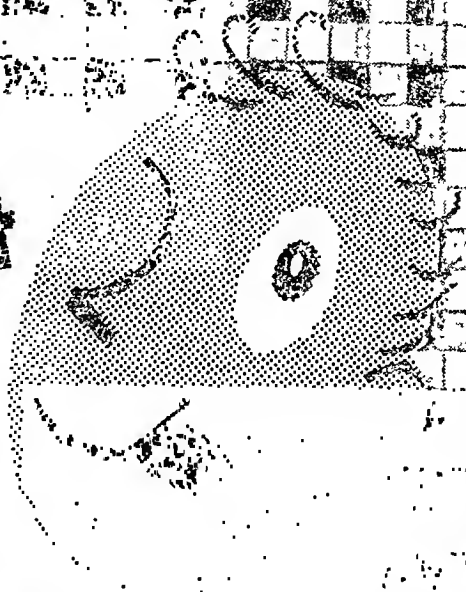
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